Blood borne infections and duration of injection drug use among young, newly initiated injection drug users

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Submitted in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy
under the Executive Committee
of the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY

2013

ABSTRACT

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The purpose of this research is to examine select baseline characteristics and drug use and sexual behaviors by duration of injection drug use among young, newly initiated injection drug users (IDUs) to better understand factors associated with risk of infection during the early stage of an injection drug users' career.

This research was conducted using questionnaire data from the Collaborative Injection Drug Users Study II (CIDUS-II), a CDC-sponsored prospective study of young (18-29) and/or newly initiated IDUs (duration of injection < 6 years). The study was conducted at six sites in five United States' urban areas: Baltimore, Chicago, Los Angeles, New Orleans, and New York City (Harlem and the Lower East Side). Investigators conducted interviews to assess baseline characteristics and injection drug use and sexual risk factors and obtained serum for testing of bloodborne infections including Hepatitis C (HCV). Duration of injection was calculated from the age of first injection to age at the time of the interview and roughly divided into tertiles by duration while maintaining years as whole numbers: 0–1 year, 2–3 years, and 4–6 years. Among the 1836 participants included in the analysis, 34% (n = 619) had been injecting for 0–1 year, 38% (n = 697) for 2–3 years, and 28% (n = 520) for 4–6 years.

Overall HCV prevalence was 34%. By duration of injection, HCV prevalence differed by site of recruitment. In Baltimore for blacks HCV prevalence increased from 33.3% among IDUs injecting <2 years to 79% among IDUs injecting 4-6 years. HCV prevalence in other cities (Chicago, Los Angeles, New Orleans and New York) showed less difference by duration. By racial and ethnic group, HCV prevalence was higher in blacks than non-blacks (=80% white) in all cities (OR = 1.43, 95% CI: 1.00 – 2.05) except Baltimore where prevalence was higher in whites (OR = 5.20, 95% CI: 2.94 – 9.18) than blacks (OR = 2.52, 95% CI: 1.38 – 3.07) as compared to whites in all other cities. The IDU groups of <2 years duration (*n* = 691) and 2–3 years duration (*n* = 697) had higher odds than the 4–6 year group (*n* = 520) of reporting injecting with others (Odds Ratio, OR = 1.52, and OR = 1.47, respectively) and injecting on average more now (OR = 1.44 and OR = 1.44, respectively). The associations remained after multivariate adjustment for demographic variables. In addition, the frequency of several other important risky injection practices were found to be higher among more newly initiated including indirect sharing (sharing of cookers, cotton and rinse water) and backloading, and certain preventive behaviors was found to be lower among this group as well, including use of new needles and NEPs. Duration of injection did not appear to be associated with sexual risk behaviors such as giving or receiving sex for money or drugs or frequency of condom use with sex partners.

These data confirm high prevalence of HCV soon after initiation of injection, and increases in HCV prevalence by duration of injection that differed across U.S. cities and by racial/ethnic group. In addition, these data provide support to the ongoing discussions about increased risk among young, newly initiated injection drug users, with risky injection practices higher among more newly initiated IDUs. These findings help to improve our understanding about the periods

of increased risk and provide important information about certain baseline characteristics and injection practices among young, newly initiated IDUs -- essential data to consider when developing risk reduction programs.

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ACKNOWLEDGEMENTS

Over the past several years, I have received invaluable support and encouragement from a great number of individuals. First and foremost, I would like to express my sincerest thanks and appreciation to my mentor and thesis advisor, Dr. David Vlahov. Dr. Vlahov has always provided insightful, sound, and thoughtful academic and personal support. I am deeply indebted to him for his unwavering commitment to my completion of this dissertation, even after so many stop and starts by me over the years. Dr. Vlahov never let me lose site of the finish line (and even "followed" me to San Francisco to make sure I crossed it!).

I would also like to thank the members of my thesis committee. Thank you to Dr. Crystal Fuller, who has participated in the committee since my proposal defense many years ago and kindly assumed the chair position in the last year. I appreciate her expert advice and strong leadership of the committee. I would also like to thank Dr. Wendy Chavkin, both committee member and dear friend, for her steadfast support over the years and insightful comments and editing advice that helped better refine the dissertation. In addition, I would like to thank the two newest committee members, Dr. Donald Hoover and Dr. Danielle Ompad for their willingness to join the committee in the last year. They both provided thoughtful feedback and instructions resulting in great improvements in the dissertation overall.

Thank you to the Department of Epidemiology, in particular Dr. Leslie Davidson for her ongoing support, encouragement and advice, and Liliane Zaretsky, for guidance and aid in navigating the cumbersome process. I truly appreciate the Department's commitment to helping me see this dissertation through to completion.

I am also thankful to CIDUS-II and all of its study participants; I am appreciative of the access I was given to this important dataset. In particular, I would like to thank the CIDUS-II site lead investigators for their feedback and advice in the analysis and writing of the manuscripts.

I would also like to recognize Dr. Laura Esserman, my boss, mentor and friend, for her ongoing efforts to make sure I finished, even requiring my attendance at mandatory dissertation writing sessions in her dining room on Saturday afternoons.

Finally, I am indebted to my family, especially my husband Eric, for the steadfast support and encouragement throughout this extended process. I also want to thank my father and role model, Dr. Nathan Becker, whose life has been one of hard work and perseverance, dedication and service to others. His passion for medicine and the betterment of others has fueled my desire to pursue a career in healthcare.

DEDICATION

This dissertation is dedicated to my sons, Brody and Colby, who have inspired me to set the right example by showing them that no matter what obstacles you face, it is important to finish what you start…even if it takes you 10+ years.

INTRODUCTION

Since the start of the HIV epidemic, injection drug users (IDUs) have been one of the most significant groups at risk for acquiring HIV. In the United States, IDUs account for more than one-third of the cases of AIDS (1). Worldwide, the epidemic has affected IDUs in Europe, Australia, Asia and Africa (2) In the United States, ethnic and racial minorities are the most widely affected by IDU-associated HIV and other blood borne pathogens such as Hepatitis C (HCV). HIV and HCV prevalence is greater in Hispanic IDUs than blacks and whites, and HIV prevalence is greater in blacks than non-Hispanic whites (3, 4).

The main factor associated with the transmission of HIV infection among injection drug users is the sharing of injection equipment. Studies early in the HIV epidemic showed that using shared, unsterile needles and syringes carries a high risk of HIV infection (5-8). Additional research has also shown that indirect sharing, such as the sharing cookers (i.e., bottle caps, to mix and heat drug into solution) and cottons (cotton placed in cookers to filter out residual particulate matter) can increase risk of infection (9). Drawing blood into the syringe before injection to assure needle is in the vein, mixing the drug with the blood, transferring drug from one syringe to another through the front-end or back end of another syringe -- these practices along with the use of other equipment by multiple users may allow a sufficient amount of the virus to remain in the needles, syringe, cookers and cotton. If equipment is shared with another injector, transmission is possible. Water used for mixing drugs and bleaching equipment may also have blood present (9, 10), and sharing these items may increase the risk of infection. Additional injection practices that increase opportunities for exposure and have been associated with HIV infection include

attending shooting galleries and having multiple trainers before being able to self-inject (11, 12). Since most HIV infections among injection drug users seemed the result of certain injection practices, early in the epidemic risky sexual behaviors were not considered a consequential method of transmission among injection drug users (13). But additional studies have shown that sexual transmission is a contributor to HIV transmission (14, 15).

HIV prevalence has also been shown to be associated with age and duration of injection. While there is no firm definition of the newly initiated injector, researchers define the newly initiated injector by duration of injection drug use, using various time frames-- less than two years, less than five years, and less than ten years. Definitions of young or younger IDUs vary as well, with age limited to under 25, 30 or 40. These definitions are more of a statistical construct than a theoretical one. In addition, duration and age are often used as proxies for one another, but they are not necessarily synonymous. While many studies show initiation of injection drug use being most common in persons in their early 20s, some studies have shown new injectors in their 40s (16).

Originally, researchers theorized that the prevalence of HIV among new injectors would be lower than longer-term users because of the shorter duration of potential exposure. Researchers thought that new injectors were less likely to share equipment and if they did so, they were more likely to share with other newer injectors, who were less likely to be infected. Plus, if people started injecting despite the knowledge that HIV can be spread through the use of shared equipment, it was hoped that they would follow safer injection practices (17). One noteworthy early study showed higher rates in older versus younger IDUs (17). Some additional studies

have also showed low rates of infection for more newly initiated injection drug users followed by a gradual increase in rates of blood borne infections for longer term users (18, 19).

But several studies of HIV and HCV seroprevalence and seroincidence found newer injectors are at the greatest risk soon after initiation of injection (20-25). Results from these studies showed younger IDUs have a 2 to 3-fold risk of HIV or HCV infection as compared with older IDUs.

In addition, one study showed that more newly initiated injectors were almost 3 times as likely to inject with someone 5 or more years older (OR = 2.99, 95% CI, 1.43-6.23)(26). Diaz and colleagues also report in a study of Latinos in New York City being given the injection by someone who was 5 or more years was associated with HIV infection (27). Contact with these older users early in the injection career might be the reason for the high infection rates in younger injectors.

In a study of drug injectors recruited from locations where drugs were being sold openly, researchers found that more experienced users were taking more precautions than new injectors. As duration of injection increased so did the percentage of injectors who engaged in less risky behavior -- 16% of injectors of less than 2 years changed their behaviors to reduce risk, compared to 29% of injectors of 3-5 years, 33% of injectors of 6-10 years and 66% of injectors of greater than 10 years (28).

This dissertation will examine the prevalence of behaviors by duration of injection drug use to observe if these behaviors parallel the literature of infection by duration. We hypothesize that

newly, initiated IDUs are more likely to engage in riskier and less likely to engage in safer sexual behaviors and injection practices earlier in their injection career than during the later stages of their injection career. In addition, this study will examine race/ethnicity and site of recruitment by duration of injection, and we expected to observe differences by race with higher prevalence in blacks than whites.

These findings may provide additional insight into an ongoing debate about risk of infection during the early stage of an injection drug users' career and better inform the development of prevention strategies among young, newly initiated injection drug users.

The specific aims of the study are as follows:

1) Review the literature on methodological issues associated with studying young injection drug users, including sampling, measurement and design issues (Chapter 1)
2) Identify correlates and risk factors of HIV among young, newly initiated IDUs (duration of injection $\leq$ 2 years) and longer-term users (duration of injection > 2 years - 6 years), including demographic factors (age, sex, race, marital status, site of recruitment, etc), sexual behaviors (trading sex for money or drugs, IDU-partner, condom use, etc), and injection practices (sharing needles and equipment, frequency and location of drug use, etc.) and to compare and contrast the above correlates of HIV and HCV seroprevalence by duration of injection drug use (Chapter 2)
3) Examine the prevalence of HCV by duration of injection (0-1 year, 2-3 years, and 4-6 years) among individuals who injected for 6 years or less by race/ethnicity and site of recruitment, and examine ORs (and 95% CIs) for the association between prevalence and

duration of injection, race, and site of recruitment and select demographic and injection behaviors (Chapter 3).

To address these aims, we plan to make use of questionnaire data from the Collaborative Injection Drug Users Study II (CIDUS-II).

The original CIDUS study was conducted to look at the natural history of HIV infection among IDUs. The study was conducted in 5 US cities, Baltimore, Chicago, Los Angeles, New York (Harlem and the Lower East Side), and San Jose. The results of the study showed higher incidence in younger IDUs as compared to older IDUs (29). These data suggest that there may be behaviors early in the injection career that increase the risk of injection during this period.

In response to the interesting findings of CIDUS, CIDUS-II was conducted to identify the prevalence and correlates of HIV infection among young (18-30) and newly initiated IDUs. For this study, one site was dropped from the CIDUS project, San Jose, and another was added, New Orleans. Factors associated with HIV included having numerous partners, identifying as gay or bisexual having been sexually assaulted, trading sex for drugs or money following initiation, and having more than 2 trainers before being able to self-inject (11, 21). The results of this study appear to confirm that higher levels of risky behaviors are present soon after onset of initiation. Further evaluation of risk-taking behaviors of these young injectors is needed to explain the patterns of seroconversion seen in this study. Additional research is needed to determine if certain risky behaviors are elevated early in the injection career and then subside as the injection career progresses.

This dissertation presents a review of sampling and study design issues for hidden populations (Chapter 1). Chapters 2 and 3 provide the results of the two analyses conducted using the CIDUS-II data – one to determine if young, newly initiated IDUs are more likely to engage in certain injection practices and sexual behaviors earlier in their injection career than they would as longer-term users and the second to analyze the relationship between prevalence of bloodborne infections such as HCV and duration of injection drug use. The final section will integrate the information presented; provide conclusions and the public health implications of these findings.

CHAPTER 1

Methodological Issues for Young Injection Drug Users

HIV and Hepatitis C (HCV) continue to be major public health issues within the US and worldwide. From the beginning of the HIV epidemic, injection drug users (IDUs) have been considered one of the most significant groups at risk for contracting HIV. In the U.S., IDUs have directly or indirectly accounted for more than one-third of the cases of AIDS, and 80% of IDUs with HIV also have HCV (1, 30). The HIV and HCV epidemics among injection drug users has become world-wide, affecting Europe, Australia, Asia and Africa (2). Early studies have shown that young, more newly initiated IDUs have higher rates of HIV than more experienced users (Vlahov et al., 1990; Vlahov et al., 1991; van Ameijden et al., 1994; Fennema et al., 1997). Consequently, these younger users constitute an important population to understand, but researchers face challenges when studying this hidden population due in part to the illegal nature of their behavior.

Thus, studies on young IDUs raise a number of methodological issues that are not present when studying a more known and less stigmatized study population. Epidemiologists in the field of HIV and HCV research face several important methodological issues including sampling issues, concerns about self-reported behaviors, and biases common when studying hidden populations. A good sampling strategy, reliable and valid self-reported behaviors, and appropriate and well-designed studies are necessary to obtain unbiased estimates of risk behaviors and their associations to blood borne infections among this population.

This section will include a description of and challenges associated with sampling methods employed by researchers studying injection drug using populations. It also will include a discussion of other methodological issues, including the reliability and validity of self-reported data, issues of bias among hidden populations, and study design issues. While these methodological issues are encountered when studying other hidden populations, this discussion will focus on injection drug users specifically.

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Hidden Populations

Some studies use the term hard-to-reach, others use hidden populations, and yet others use underserved. The term hard-to-reach is sometimes used to refer to minority groups; it has been used to refer to hidden populations; and sometimes used to refer to a wider segment of the population such as old or young persons. In addition, it has been used to refer to underserved groups, namely those that have slipped through the net of social services. The problem with using the term 'hard to reach' is that it implies homogeneity within a disparate group. In addition, it is considered a stigmatizing term since it has been associated with being obstinate, disadvantaged, illiterate, information poor, and chronically uninformed (31). For the purposes of this discussion, the more specific term hidden populations will be employed.

Hidden populations are defined as groups of people who do not wish to be found or contacted, or those who are "disadvantaged and disenfranchised" (32) . Hidden populations may also actively seek to conceal their group identity. This includes homeless and transient persons, drug users,

sex workers, criminal offenders and other street people, including mentally ill persons, as well as those that do not face such stigmatizing conditions such as undocumented immigrants.

Hidden populations are rarely included in national surveys because they do not have fixed addresses or phones or may be unwilling to participate in interviews. However, those that belong to hidden populations include those persons who are most likely to engage in drug use and acquire blood borne infections such as HIV, Hepatitis B and HVC. In other words, those that are least understood and studied are in the greatest need of information regarding risk behaviors and prevention efforts.

Sampling Issues for Young, Injection Drug Users

There are two primary reasons for taking a sample instead of attempting to measure the entire study population: feasibility and ease. It obviously is more efficient and requires less time and money to collect data from a sample rather than the entire target population. In addition, greater attention can be focused on ensuring high-quality, reproducible measurements if they are made on a smaller number of individuals. Sampling options can be divided into three general categories based on how the samples were collected: probability sampling, representative sampling and non-probability sampling. Depending on the sampling methodology utilized, there may be tradeoffs between representativeness/generalizability, reproducibility and convenience.

Probability or Representative Sampling

Probability sampling, or random sampling, is based on probability theory, and each person in a target population has a known non-zero probability of selection (33). This type of sampling is considered the gold standard by which other sampling methods are compared for accuracy. Probability sampling is a method of producing an unbiased estimate that can be generalized to the target population. In representative sampling, the population is divided into strata or subpopulations with characteristics of importance for the research, e.g., gender, social class, education level, religion, etc. Random samples are taken of each stratum. Important characteristics are distributed similarly in both the sample and the population. Stratified/representative samples are as good as or better than random samples because they improve the potential for the strata or characteristics of interest to be more evenly spread over the population, and thus these samples can provide better precision and require a smaller sample size, and thus less time and money. However, representative sampling requires detailed knowledge of the population characteristics in advance, so the strata may be more difficult to construct.

Probability sampling and representative sampling models have been used to study trends in behaviors including drug use among youths. For example, the Youth Risk Behavior Surveillance System (YRBSS) was designed to monitor health risk behaviors (injuries; tobacco use; alcohol and other drug use; sexual behaviors; dietary behaviors; and physical activity) among youths and young adults (34). The YRBSS includes national, state, and local school-based surveys of high school students. The national school-based survey employed a three-stage sample design to produce a nationally representative sample of students in grades 9-12. This sampling design allows inferences to be made about youths who attend school only and, therefore, is not

representative of all persons in this age group. Thus, a major limitation of this study design is that it will not capture a measurable group of young people who do not attend school, and out-of-school youths are more likely than those attending school to engage in the majority of health-risk behaviors (35).

Selecting probability or representative samples of young injection drug users may be prohibitively expensive in terms of time and money as well. While, these sampling methodologies are well-suited for the general population, they are often not a viable option around drug-using populations because potential legal ramifications deter cooperation, an extremely large sample size is required to capture such a rare event, and given the hidden nature of this population, a study of this kind would miss out on important segments because they are not easy to locate nor do they live in stable locations (36). Thus, this model of sampling would be an inefficient method for capturing at risk youths, particularly young injection drug users.

Non-probability Sampling

Although probability sampling is considered more accurate and rigorous, given that it is not always practical or feasible to do probability sampling among drug using populations, researchers have employed non-probability sampling methods, since they are designed to better capture hidden populations. Non-probability sampling does not include the random selection of study participants. In non-probability (purposive) sampling, the sample is selected in such a way that the chance of selecting each unit within the population or universe is unknown. The selection of the subjects is arbitrary or subjective, since the researcher relies on his/her

experience and judgment. As a result, there are no statistical techniques that allow for the measurement of sampling error. Non-probability sampling causes difficulty in generalizing study results; however, it is more practical and feasible since the researcher relies on readily available groups or units of study, and efforts can focus on obtaining subjects who may not be captured using standard probability sampling and representative sampling techniques. Examples of non-probability sampling techniques include institutional, community-based, snowball and chain referral, targeted, time-location and respondent drive sampling.

Institutional sampling methods

Some of the earliest studies on HIV and injection drug users involve subjects' recruited in institutions including prisons and drug treatment centers (7, 37-41). Consecutive sampling and convenience sampling are often used in these settings. Consecutive sampling involves sampling individuals with a given characteristic as they are presented until enough with that characteristic are acquired, for example, every individual entering a given institution within a pre-defined time period. Many prison-based studies of injection drug users utilize consecutive sampling because it can be quick and efficient. Plus, there is some generalizability to the sample of incarcerated IDUs because studies have shown stability of HIV seroprevalence in prison entrants. In other words, consecutive sampling for a short duration may be representative of the overall incoming prison population (42). However, generalizability to the overall IDU population may not be appropriate given that this sample may not be representative of all IDUs, even though a number of injectors do report a history of incarceration (43). Another major limitation of using a prison-

based sample is that these participants may not provide a detailed history (in particular, a detailed drug history) for fear of self-incrimination for crimes for which they have not been sentenced.

Convenience samples are also often utilized in the prison system. A convenience sample is a non-probability sample in which patients are selected in part or in whole at the convenience of the researcher. Researchers use individuals who are available rather than selecting from the entire population. Because some members of the population have no chance of being sampled, the extent to which a convenience sample – regardless of its size – actually represents the entire population cannot be known. Therefore, the results obtained cannot be generalized to the broader drug using population, because it is difficult to determine which biases exist. In addition, reproducibility is difficult. However, convenience samples are often used in the prison setting because of the relative ease of implementation. This method allow for a convenient method of investigating a problem.

Studies using subjects in drug treatment are also often conducted with consecutive or convenience sampling methods. As with prison-based samples, treatment samples are obtained relatively easily and inexpensively. It is estimated that only 15%-20% IDUs in the United States are enrolled in drug treatment at any given time (4), so studies based primarily on in-treatment populations may contain substantial biases. HIV risk may change over time and not be reflective of the general population as interventions from the treatment program are implemented. These studies tend to oversample motivated individuals, and those willing to participate may differ from those who are not. Also, those who enter treatment as opposed to those who avoid treatments may differ in significant ways. Studies using drug treatment samples also tend to

undersample cocaine users because drug treatment programs tend to focus on the treatment of heroin addiction through methadone maintenance programs (38, 44). In addition, young, newly initiated IDUs have limited connection to drug treatment services, because programs usually require that clients have a well-established drug habit to receive treatment. So, drug treatment samples tend to primarily include IDUs of longer duration (44-46). In fact, studies have shown that IDUs not in treatment were more likely to be male, younger and black than those currently in treatment, and to have started injecting drugs more recently (45-48). When attempting to sample younger populations for a rare trait such as injection drug use, using health clinics or drug treatment clinics may not be appropriate since as previously noted, younger populations are less likely to use these services.(46) Any study that relies heavily on capturing young IDUs from these programs may not accurately represent this population of IDUs.

Community-based sampling methods

There are limitations to institutional sampling, and probability sampling methods are difficult to conduct with hidden populations such as IDUs. To address the various challenges of sampling encountered, researchers have used several different methods of community-based sampling for injection drug using populations. Some of these strategies are better than others for reducing bias. Although these methods are less than ideal from a theoretical standpoint, since the extent to which it actually represents the entire population cannot be known, community-based sampling methods are often necessary since traditional sampling methods are not likely to yield representative samples of the population of interest.

Snowball sampling and chain referral sampling

Snowball sampling is a non-probabilistic form of sampling in which persons initially recruited for involvement in a study are then used as informants to locate other eligible persons. New cases are recruited through a process of onward referral from known cases. Sampling starts with one or more known individuals who meet the given criteria. They are interviewed and asked to recommend other potentially eligible subjects and facilitate introductions to these people. The recommended persons are then contacted and interviewed, and the process repeated. The sample thus expands by tapping the social contacts and networks of, in this instance, IDUs (49). The foundation of this method of sampling is that members of a special or rare population tend to know others from that population. Snowball sampling can be advantageous when the focus of the study is a sensitive issue such as drug use. Since the information is obtained from the initial individual and the contact is made possible by this individual, the atmosphere can be one of trust for their peers (50).

Chain referral sampling is quite similar to snowball sampling; it relies on participants to refer others who have similar areas of interest or experiences. Multiple networks are accessed through multiple snowballs in order to broaden the scope of the study to more than one social network. There are limitations to using either snowball or chain referral sampling methods. First, the representativeness of the sample is unknown and thus there may be issues of selection bias, sample bias, and non-independence of sample units (49). For example, a sampling design that recruits IDUs primarily near needle exchange programs may bias the sample toward IDUs who engage in less risky behaviors. Moreover, if the sample is acquired through a particular social

network, the study sample may under or over-represent younger or older IDUS should the initial contact's network of friends be quite similar in age and duration of injection. In addition, since the sampling method is based upon referrals, subjects with larger networks will be oversampled. Finally, a study of this nature can be time-consuming and demanding on fieldworkers.

Targeted sampling

Targeted sampling, developed by Watters and Biernacki, is a " purposeful, systematic method by which controlled lists of specified populations within geographic districts are developed and detailed plans are designed to recruit adequate numbers of cases within each of the targets" (51). First, ethnographic mapping is conducted to locate and identify various networks or subgroups of interest. Then, probability and non-probability techniques (such as snowball sampling, stratified sampling, and quota sampling) are utilized so a given number of people with very specific characteristics are systematically selected from an identified subgroup. Targeted sampling was created through the work of Watters and Biernacki on HIV and injection drug users in high-risk areas of San Francisco. Because it is not a true probability sample, there are some concerns about bias. Depending on the recruitment strategies employed and the time and location of the sampling, the researchers may end up with just a subset of the population of interest, e.g., a final sample that is dominated by unemployed IDUs while excluding more middleclass users, who may be at work during the times of recruitment (51). The strength of targeted sampling is that although it is not a probability sample it is not a convenience one either. There is a strong initial effort to locate and describe the population using ethnographic mapping, a powerful tool for locating hard to reach populations like IDUs. Targeted sampling can be a useful method for

constructing reproducible samples, and ones that are comparable in terms of demographics and risk behaviors across other cities and communities as well.

Time-location sampling

Some hidden populations tend to gather in certain known locations. As a result, time-location sampling can prove to be an advantageous approach to locating these groups and creating generalizable estimates for these hidden populations. Time-location sampling is a method in which specific venues are the sampling units. First, pre-surveillance assessments or preliminary ethnographic mappings of potential venues in which hidden populations are known to congregate are identified. Then, a random sample of venues from the universe of potential venues is selected, as is the time and date, and then those persons attending those randomly selected venues at those randomly selected dates and times are systematically approached (52, 53). By targeting recruitment efforts to known locations where hidden populations congregate, studies can better concentrate their resources and efforts.

Time-location sampling has been used effectively recently to study HIV and HCV prevalence and risk factors in “red light” districts for sex workers (54, 55), bars for men who have sex with men (52, 53, 56), clubs for the youth drug culture (57-59) and public venues near fast-food restaurants, subway stops and recreation areas for orphaned and homeless youths (60-62).

Since this method involves approaching potential participants in public venues such as shooting galleries and clubs, it can present with its own set of challenges. Potential participants are

usually engaged in other activities, and the venues offer little, if any, privacy so the accuracy of self-reported information obtained during these interviews is unknown. In the Young Men's Survey in San Francisco, less than half of subjects approached were eligible, and, of those, only 61% participated (56). However, in a more recent study of Latino men who have sex with men, 82% of eligible men participated and sexual risk behaviors reported were similar to other studies of similar populations conducted using other sampling strategies (53).

Street-Intercept Method

The street-intercept survey technique is a method in which interviewers recruit and interview strangers in locations in which the target group is thought likely/expected to be found. The goal is to capture a representative sample of the eligible population within a specific catchment area. Interviewing sites are based within a sampling unit, such as a street block. Oftentimes members of the target group of interest are used as "peer" interviewers. Street-intercept methods are useful for specific harder to reach populations for focused studies, for example, for studies of high-risk issues such as young injection drug use or HIV. In certain instances, interviewers have been instructed to interview the first eligible person anywhere in the target area (63) or to preferentially target certain members of the population (e.g., for every 10 interviews, at least 3 should be women and 3 should be 16-18 years of age) (64, 65), or to systematically recruit a sample of the relevant populations (e.g., approach every fifth person who passed (66).

Street-intercept sampling is more cost-effective in urban areas, since highly dense areas are more likely to yield target populations more rapidly and in less time. In addition, studies have shown

that the street-intercept method has a high response rate and high interview completion rate (63). One problem that has been faced using this method is that the peer interviewers may be reticent to interview strangers due to the interviewer's concern about identifying him/herself as an injection drug users publicly or asking others to identify themselves (64). In addition, the representativeness of the sample for that catchment area is also unknown. Street-intercept studies have been shown to potential over-represent homeless and unemployed person (63, 66), but the successful access to hidden or hard to reach populations could be considered an advantage of this survey technique,

Respondent driven sampling

Respondent driven sampling (RDS) is another method for locating and obtaining hard-to-reach populations. Developed by Heckathorn while doing work in HIV prevention among IDUs in Connecticut, RDS is a modified version of chain referral or snowball sampling, with a mathematical weighting system utilized to assist with the fact that the sample was not drawn from a simple random sample. The sample is composed through systems of social networks with the assumption that the best people to access subjects from hidden population are their own peers (67). A primary characteristic of RDS is that it is based on a series of incentives -- rewards for participating in the study and additional rewards for recruiting others. To avoid issues of confidentiality, participants are not asked to provide names; they are given coupons and then provided rewards if the coupons are used by others who are recruited to the study. This method is systematic and can be reproducible in other communities in an attempt to obtain comparable samples.

The statistical theory upon which RDS is based implies that if the peer recruitment process proceeds through a large number of waves then composition of the sample become independent of the seeds from which the recruitment was initiated. However, if a group is smaller or more isolated, and the network is very homogenous, recruitment chains move slowly and may not be able to move across group boundaries. Thus, RDS appears to be more helpful in some places and populations than in others (67).

Even though the recommended sample size is twice as large as would be needed under simple random sampling (68), RDS has advantages in terms of collecting the required sample size in a short period of time (69, 70). In a study among IDUs in Albania, the researchers started with 13 to 15 seeds, and recruited 200 IDUs within 8 weeks (71). Another study in NYC found that they were able to recruit 118 more drug users than originally proposed in 25% of the time (70). However, other researchers have faced more challenges with sampling using RDS. Within a study of sex workers in Eastern Europe, researchers were unable to attain sufficient samples due to the specific make-up of the network. These included the low density of sex workers in the region combined with the lack of social networks between the sex workers, limited number of venues, and limited contact between sex works and local services (72). But, overall, RDS is efficient with respect to time and economics. It is effective in recruiting a diverse sample and provides methods for getting interventions to hidden members of the community (57). As is the case with all non-probability sampling methods, limitations exist with this approach that may be due to network characteristics (e.g., success is predicated on the existence of larger, more dense social networks) and concerns about whether enough area has been covered.

To reduce issues of oversampling from larger networks, recruitment quotas and special incentives for subjects whose traits are associated with smaller networks have been utilized. In addition, Heckathorn reports that if the sampling process is allowed to go through enough iterations, the final sampled population should be independent of the initial subjects recruited (67). At the point when the recruitment process goes through enough waves the sample reaches equilibrium (i.e., the population demographics stays fairly constant), it is assumed that the final sample is representative of the underlying population with regard to demographic factors. In a study utilizing three US cities and St. Petersburg Russia, the estimates for one of the four cities (Los Angeles) differed from the other three (73). In examining the reasons for this discrepancy, the answer lies in the recruitment pattern by gender, with each gender under-recruiting members of the opposite gender. Although men reported knowing 24% females, only 6% were recruited. In contrast, a recent pilot study of RDS for recruiting injection drug users in New York found cross-gender, race, and ethnic recruitment indicating that RDS is an effective tool for recruiting a diverse group of injection drug users in behavioral studies (74). But, it is difficult to confirm the representativeness of the sample captured since there is no gold standard method for measuring actual network composition.

Researchers have focused on ways to increase the speed of reaching equilibrium by improving peer recruitment. While most studies focus on individual factors that affect peer recruitment (74-77), one recent study focused on individual, study and neighborhood characteristics and conducted group training sessions of participants to improve peer recruitment (78). The study found that both study-level (e.g., attending training sessions) and neighborhood-level (e.g., being

recruited in neighborhoods with more positive attitudes about drug use) characteristics improved peer recruitment.

RDS was developed to avoid the problems and biases associated with other community-based sampling methods. The safeguards that have been put into place to prevent ethical violations include: limited compensation for participation and recruitment of others (e.g., through referral quotas), minimization of pressure to participate since study team members not peer recruiters obtained informed consent and administer the interview, and no mention of payment in recruitment ads or coupons (79). Even with the inclusion of such precautions, ethical issues can arise. One ethnographic study that attempted to document a 4-year qualitative study of RDS among IDUs in Chicago found that people eager to participate for monetary reasons identified methods for circumventing the screening procedures, and an "underground marketplace of selling coupons emerged" (80). However, the study's findings were critiqued in a series of responses (81-83), which questioned several methodological issues with the analysis, including biases in the sampling, eagerness to accept the respondents comments as "truth,' and ignoring the researcher's own impact on what was observed (81-83). In addition, one assessment argued that the issues raised by the author were not new to RDS but were issues faced by all community-based outreach methods utilizing payment for hidden populations (81). Semaan, et al. reviewed scientific, ethical and regulatory literature of RDS to determine if practices that are commonly utilized for RDS for IDUs are appropriate (79). Semaan et al. found remuneration for participation was appropriate for the time and effort in recruitment, and the literature did not support concerns that payments would be seen as a means to purchase drugs and this would somehow compromise the integrity of the participants. In addition, investigators provided

strategies for overcoming the challenge of maintaining participant confidentiality regarding infectious disease status, while ensuring the health of network members. Study staff counseled participants on the possibility of infected partners and the need for safe behaviors and risk reduction strategies that involve a hierarchy of methods that range from stopping drug use, to sterile needles for each injection, to using their own equipment without sharing.

In direct comparisons between community-based sampling methods, some studies have found that RDS, targeted sampling and chain referral sampling all performed well (i.e., all methods yielded samples that were similar in terms of many demographic characteristics such as age, race and sex) despite specific limitations of each (77, 84). Other studies have reported differences in demographics such as SES and risk behaviors such as level of unprotected sex (85, 86); however this may be due to variability in recruitment period and geographic location. One concern about targeted sampling is that the method may not allow for the recruitment of a population that reflects the general IDU population, but rather one found during the times of recruitment (77). In a study among female sex workers in Asia, the study employing RDS found success at reaching more inaccessible female sex workers (87). More hidden populations appeared to be receiving education and testing equally to more visible female sex workers. Networks were dense and diverse enough to provide a large sample in a short amount of time. By using RDS the less visible members of the population were included.

Safety of the researchers may also be a concern for targeted and chain referral sampling since these methods oftentimes are conducted in unfamiliar areas and the interviewers may be carrying money for the financial incentives, whereas RDS is usually conducted in a storefront, a fixed site

in which a certain number of staff is usually present. Weather conditions can also hamper the success of targeted and chain referral sampling since these methods are conducted outdoors. RDS appears to be more practically advantageous – greater recruitment efficiency and safety of the staff and respondents (69). RDS required less staff time per recruited respondent and resulted in a higher proportion of eligible subjects among the screened population as compared to targeted sampling (84). However, RDS subjects were often offered higher incentives for participation, so it appears to come at a greater cost (84).

Since young, newly initiated IDUs are often difficult to locate and recruit for studies because of their hesitancy to self-identify and their limited connection to health care and drug treatment services, utilizing random or institutional sampling frames would not be the most productive methods to capture this population. In CIDUS-II, the study utilized community-based convenience sampling methods to recruit participants. Certain sites (Lower East Side of New York, Harlem and Baltimore) used ethnographic mapping to identify areas in which drug using and selling were particularly prevalent, whereas other sites (Chicago and Los Angeles) did not use formal mapping but rather targeted sampling.

Additional methods were used for recruitment including: informal chain referral; advertisements in alternative newspapers (Chicago); flyers posted at college campuses (Chicago), emergency rooms (Baltimore), health clinics (Baltimore), youth shelters (Baltimore), and needle exchange programs (Chicago, Baltimore, Harlem); and distribution of information in areas with high prevalence of young drug users (Lower East Side of New York). Baltimore, Los Angeles and Harlem used mobile clinics to increase their accessibility. Chicago also contacted participants

through respondent-driven sampling, and participants were given 3-6 coupons for distribution to other young IDUs.

Without a sampling frame, the extent to which this sample truly represents young injection drug users in general or even within the cities studied remains unknown. But, given the several different methods employed by the researchers to recruit subjects, the intent was to cast as broad and comprehensive a net as possible given the potential barriers. The demographic characteristics of participants of this study are similar to the characteristics of drug users recruited in others studies. The majority of participants recruited on the Lower East Side of New York were male (64%) and white (76%), and this is consistent with other studies conducted in this area (74, 88). Demographics in previous studies in Baltimore were consistent in terms of race (67% were black), but quite different in terms of sex. Previous studies have reported a high proportion of males (ALIVE = 64% to 79% males), but CIDUS-II reports less than 40% males (21). Thus, to offset the potential limitation, inferences are made with caution.

Measurement issues for studies of young, newly initiated injection drug users

Although researchers may be able to verify injection drug use by the presence of physical evidence (i.e., “stigmata” or track marks), they must frequently rely on self-reported behaviors of IDUs in studies involving drug use. It is often the only method researchers can use to study injection practices, sexual behaviors, and undetected criminal activities since measuring drug use among illicit drug users by other more validated methods such as urinalysis or other biologic assays is often not feasible or informative enough (e.g., detection time is limited for blood and

saliva to less than 48 hours, and individual differences in hair including length, cleanliness, and bleaching can affect the concentrations detected in hair) (89). Given the dependence on self-reported behaviors, there are concerns about the reliability and accuracy of the information gathered through this method.

Reliability

Reliability, the extent to which results of a measurement can be replicated, can be operationalized in several ways in studies of injection drug users. Common methods include test-retest reliability (the same measure is administered to the same individual at two different time points) and internal consistency (behavioral questionnaires can include the same or similar questions more than once, or multiple interviewers can ask the same question). Overall, the data suggest that drug users are reliable, and their responses do not vary much over time ($r = 0.71$-0.94) (90-94). In fact, one study found that there was consistency of response of heroin users after several years of follow-up (91, 95). Pairs of IDUs who have been interviewed about shared behaviors have also been found to have high levels of agreement (93, 96). In addition, Schutz et al. reported that self-reported injection frequencies for different time periods covered during the same interview (1 month vs. 6 months) had high levels of concordance (97). A recent meta-analysis that looked at the reliability of self-reported information at 1, 3 and 6 months showed that all recall periods showed good test-retreat reliability with shorter time periods being the most reliable for drug use behavior (98). Although high levels of agreement have been shown, there is not complete concordance, as memory is not perfect and inconsistencies are expected.

Validity

It is possible that self-reported behaviors can be reliable but not valid if the drug user can continue to repeat the same misinformation, in other words, the drug user is a “reliable liar ” (92). One major form of validity is concurrent validity—agreement between the self-report and another measure of the same question. Validating self-reports requires that the information be compared to some other more accurate method. There are several methods for analyzing drug metabolites in biological specimens including urine, blood, perspiration, and hair (99, 100). Each method offers somewhat different information about patterns of drug use over time. Urine tests will test positive within a few hours of drug use and typically show more recent drug use. While false positives are rare, the risk of false negatives can be high since masking agents can be ingested and clean urine can be substituted (89, 101). Blood tests, while more invasive and costly, are considered extremely accurate and can provide proof of drug use within hours (101). Hair sampling is conducted by cutting a section of hair close to the scalp. The greatest benefit of using a hair sample is that, depending on the length of hair, drug use can be analyzed over an extended period of time (100, 101). Although hair analysis can provide information about drug use over a several month period, it is not without its limitations. Several studies exist about the potential of ethnic bias in hair testing due to findings that drug absorption into the hair varies due to melanin content (100, 102, 103). In addition, participants may have no hair/shaved heads, use shampoos/washes to eliminate some of the metabolites, as well as chemically process their hair (straighten and/or color), all of which may affect the results of these assays (101, 104).

In addition to biological assays, methods for validation of self-reports can include criminal justice and treatment program checks and reports from family members, close friends, and drug using partners (93, 105).

Overall, the literature suggests that there is variability in the validity of self-reports as a result of survey conditions, types of drugs used, type of measure and the characteristics of the sample population (106, 107). Harrison reviewed the literature on self–reported drug use, and before the mid-1980s validation studies suggested that drug use was fairly accurately reported through self-reported surveys. Some more recent studies have shown varying degrees of under-reporting depending on the population studied, with less under-reporting among participants in treatment as compared to those out-of-treatment (96, 108).

There are numerous reasons why self-reports from drug users may be invalid in particular situations. If the person feels there is a negative consequence associated with reporting certain behaviors, they may feel the need to hide the truth. These perceived consequences might include expulsion from a treatment or housing program, incarceration or threats to child custody. However, in situations in which providing the information does not have any perceived influence on future access to treatment or possible incarceration, concordance between self–reported drug use and other independent measures of drug use have been shown to be high (70-90%) (92, 96, 108). Studies that make efforts to provide anonymity and confidentiality typically have more accurate self-reported behaviors.

Research has shown that self-administered interviews and in-person interviews yield different estimates of self-reported drug use (109-111). But, given the difficult skip patterns imposed by many surveys and the expectation of somewhat proficient level of literacy, interviewer-administered surveys are often necessary. In these instances, interviewers may employ more confidential methods of obtaining participant response (e.g., interviewers may show a list of responses to questions and ask the participant to reply using the letter or number assigned to the response rather than supply the information directly). Audio computer assisted structured interviewing (Audio-CASI) has also been studied as an approach to increase confidentiality and improve self-reporting of sensitive information (112-115). In methodological studies conducted by the Substance Abuse and Mental Health Services Administration in conjunction with the National Survey on Drug Use & Health, formerly called the National Household Survey on Drug Abuse, researchers found that higher rates of drug use were reported with the use of Audio-CASI than paper-and pencil interviewing, which consisted of a combination of interviewer-administered questions and self-administered ones. This was especially evident among younger participants in the survey (116). In addition, the order of questions also helped with improving the accuracy of self-reported behaviors. Starting with less sensitive questions and moving to more sensitive ones later in the interview when a report has been established can increase the accuracy of response to the more sensitive questions. While studies have shown that the accuracy of information provided by a respondent is relative to the level of privacy afforded during the interview(117), a recent review and meta-analysis of 15 studies comparing face-to-face interviews with other tools for providing self-reported HIV risk behaviors did not find that Audi-CASI and other computer assisted techniques were consistently better at acquiring more information about risky behaviors (111).

Issues with validity of the self-reported behaviors may not solely be due to concerns about the consequences of revealing illegal information, self-reports may not be accurate because respondents simply don't remember or memory is impaired by drug use. For example, recall about first use of a substance and age at the time may fade over time. It may also be because absolute dates are often difficult to recall.

In addition, participants may underestimate time to an event, and bias may be the result of this forward telescoping -- a bias in which respondents report events closer (or further) to the time of the interview than is true. Studies have found forward telescoping in response to questions of age at first use of various substances (118). It can be postulated that young injectors may be more likely to recall the details surrounding initiation of injection drug use due to the proximity of the event as compared to longer-term users (17, 21, 22, 119, 120). However, year or age of initiation tends to be recalled clearly (121). In order to limit errors in exposure, questions can be framed using appropriate or familiar language, and questions can be ordered in a certain manner to encourage better recall. To minimize recall bias, studies have referred to other memorable biographical landmarks to help anchor the information (122).

Response bias may also be the result of socially desirable responding. In a study to determine the validity of self-reported serostatus data, researchers found that the participants who rated high on self-deception (believing positive statements even when they are not true) were more likely to alter information that may be a threat to their self-image (123). By rewording questions to reduce the propensity of responding with a social desirable response, providing incentives for accuracy of self-reporting serostatus, offering self-administered questionnaires or increasing the

rapport between the participant and the interviewer, improvement in the accuracy of self-reported data can be achieved.

Self-reported information is key to studying drug use and other risk-taking behaviors. Biological assays can only confirm drug use, but they cannot provide such important information as age of initiation, individual behaviors and perceptions about risk taking, as well as other factors that may be associated with increased risk of HIV and other blood born infections. Consequently, researchers must rely on self-report for sensitive information. As the research suggests, in certain settings in which there is a perceived level of confidentiality and privacy, self-reports are sufficiently valid to provide information about drug use and other risk-taking behaviors.

Additional issues in studies of young, newly initiated IDUs

There are additional biases often present in studies of hidden populations. The bias that results from an unrepresentative sample, called selection bias, is an area of concern in studying young IDUs. Studies show typically higher rates of injection drug use among men than women, but comparable rates of HCV (124). If women are more likely to conceal their drug use due to stigma of injection drug use, samples may be more biased in women than men. Triangulation, the synthesis and integration of data from multiple sources can help lessen selection bias.

In addition, studies of young, newly initiated IDUs will most likely consist primarily of volunteers. It is likely that these volunteers will differ from those who do not agree to participate, and those that complete the entire study may differ from those who are lost to follow-

up. Consequently the ability to generalize the results from such studies to other young IDUs is limited.

New technologies to sample and follow-up with hidden populations

With recent advances in technology and the wide availability and usage of the internet and Smartphones, researchers now have access to new methods for reaching out to hidden populations.

Studies have shown that internet usage continues to grow, with over 78% of the population utilizing the internet, including 95% of individuals age 18-29 (125). Internet research allows for access to large samples for minimal cost, increased convenience for the recruiter and participant, and increased anonymity, all of which can improve access. In addition, since the majority of the users of the internet are young, it allows for increased access to younger subjects. In a review of 46 studies that used the internet to research hidden populations, researchers found that the mean age of participants in these studies was 23 years (126). Health researchers have used the internet to collect health information (127), deliver health interventions (127-129), conduct epidemiologic studies (130, 131), and, more recently, to collect behavioral data (132, 133). Internet chat rooms, search engines, hyperlinks from specific websites offer opportunities to develop and test methods to identify and motivate the involvement of participants in web-based surveys who are usually difficult to access using traditional methods. Studies have used the internet in creative ways to access people who would be unlikely to participate in research in other settings. For example, some studies have utilized the internet and online chat rooms to get

access to men who have sex with men (134, 135). The ease of distributing questionnaires across the Internet using a variety of technologies has made this approach to conducting research particularly appealing to researchers.

When asking about socially unacceptable or illegal behaviors, interviews that are conducted in person may face serious challenges. Drug users, who are successful at hiding their drug use, may not be easily reached through snowball sampling because they would limit their contact to social networks of drug users and would be less likely to acknowledge drug use. Web-based data collection may be a more effective format to ask participants about sensitive and difficult to discuss topics. Researchers found that the majority of individuals responding to an internet survey felt comfortable answering personal questions, even some related to illegal activity. Many of the respondents even answered open-ended questions with lengthy responses (136). Using email, one can create a survey, mail it to large numbers of individuals, and receive replies quickly, easily and inexpensively. Studies have shown that the majority of subjects respond to email surveys within 3 days; however, there are some concerns about response rates and selection bias since surveys by email are not anonymous (137, 138).

Studies have found a rise in the use of mobile phones for drug dealing, trading and other contact between drug users (139). Consequently, a study was conducted to examine the efficacy of contact by mobile phone for a follow-up interview of heroin users in Malmo, Sweden (140). Researchers found that that during 15 to 21 attempted calls over a 2 year period, 68% of subjects were successfully contacted for at least one follow-up interview (average = 6.9 interviews). Although this is only one study and it still resulted in an attrition rate of over 30%, mobile phone

contact can be added to the arsenal of techniques used by researchers to reach participants for follow-up.

However, mobile phone usage varies greatly by geographic region with penetration rates as high as 65-75% in Europe and North America and as low as 19% in Asia, and there is wide variation in Africa, ranging from as high as 84% in South African and as low as 16% in Central African Republic (141-143). In addition, phone access and availability may differ by economic status, since certain marginalized groups may not have regular or ongoing access since they may not be able to consistently cover monthly costs. Consequently this mode of contact and data collection may have limited utility in certain parts of the world and among certain lower income individuals. For example, utilization of this mode of communication for conducting interviews may have limit reach among homeless youths who inject.

Smartphone technology also has improved ease and access to conducting interviews. One study recently looked at the feasibility of using Smartphone applications to increase the speed at which interviews are conducted -- questions can be asked and answered and recorded rapidly, to reduce non-response rates. In addition, given the familiarity by most people in developed countries in North America and Europe with Smartphones such as iPhones, the device can be handed over to the participants and they can move through the survey at a rate that they themselves dictate. A recent study used cell phones and electronic tablets to collect ecological momentary assessment (EMA) data from participants with drug use issues (144-146). EMA is a method that permits the research participant to report on symptoms and behaviors close in time to the experience in the participant's natural environment (147, 148). Since EMA involves repeated sampling of

participants' current behaviors and experiences in real time and in their natural environments, Smartphones allow for more flexibility and improved compliance. Researchers have also found that Smartphones and tablets simplify the process for interviewers and allows the interviewer to focus on communicating with the participant and building the relationship rather than focusing on the documenting the encounter (149) . Finally, this format allows for the use of multi-lingual surveys, even in the absence of multi-lingual research assistants, which also should help reduce non-response bias (150).

Opportunities exist for researchers to conduct research online as well. However, there are also recruitment issues using the internet. Studies have shown that educational, economic, racial and gender disparities for those who have access to the internet versus those who do not (151). For example, samples recruited online may be more likely to be male and of higher education and socioeconomic status (152). But, this "digital divide" seems to be changing since the numbers of people online increase everyday – the International Communications Union reported in June 2012 that over 2.3 billion people have access to the internet and 6 billion have access to mobile phones (153, 154). In fact, data suggest that certain groups in the US such as gay and bisexual web users include a higher proportion of participants who are lower educated, lower income, and lower employment rate (133). This variability may be due to the fact that the internet may be considered a safe place for certain marginalized groups to interact without concerns about negative consequences (154). As a result, newly initiated injection drug users, who may be less willing to self-identify as an injection drug users in more public settings, may be more willing in this more anonymous setting to share information about behaviors.

Surveys conducted by the internet and using Smartphones are potentially useful tools for studying hidden populations. These methodologies provide convenience to the participants and researchers, access to large samples at a negligible cost, and anonymity of participation and increased opportunity for follow-up. In addition, since the internet is utilized extensively by young people, it offers unmatched access to these individuals.

Design Issues for studies of young, newly initiated IDUs

In cross-sectional studies, exposure and disease status are assessed simultaneously among individuals. Cross-sectional studies may examine seroprevalence of a blood-borne infection at a particular point in time or over a specified time period such as 1 year. This study design was the method for numerous early seroprevalence studies of HIV among IDUs (155, 156). Because cross-sectional studies assess risk behavior and disease status at the same point in time, it is not possible to determine if exposure preceded outcome or vice versa. Associations dependent upon time do not typically show consistent results between cross-sectional studies and incidence studies. For example, studies have shown that longer duration of injection drug use is associated with higher levels of seroprevalence but shorter duration of injection is associated with higher levels of seroincidence (21, 22, 157). If the disease or outcome duration is not related to exposure, then a cross-sectional study can provide a relatively accurate measure of risk. Cross-sectional studies also tend to over-represent prevalent cases, and thus, the information collected is usually biased toward factors related to survival rather than etiology. However, by limiting recruitment to young, newly initiated IDUs, the effects of duration can be controlled. Cross-

sectional studies also are often easier to conduct, less expensive, and are helpful in public health planning.

Despite the relative ease of conducting cross-sectional studies, longitudinal studies should be conducted when feasible. Issues of prevalence-incidence bias can be lessened by prospective follow-up. In addition, behaviors can be followed over time to determine if initial behaviors predict subsequent behavioral patterns. Longitudinal studies provide the best method for studying the cyclical natural of drug use and addiction, but internal validity can be compromised due to high rates of loss to follow-up. Researchers are often challenged by the transitory, chaotic and hidden lifestyle that accompanies drug use. Hidden populations, as the name indicates, are often difficult to identify and locate. It is important to minimize loss to follow-up in order to reduce systematic bias and potential loss of statistical power (158). Young, injection drug users are often transient and do not want to be tracked. Standard methods to follow-up with this population will not work. Special efforts must be made to track this population. Numerous studies have been published that describe various techniques to avoid participant attrition (159-161) and several studies have produced high follow-up rates (161-164) by using proactive models (e.g., collecting complete locator information, providing incentives, using peer interviewers, and keeping follow-up interviews brief and identifying deficient information for locating subjects early). These studies also acknowledge that adequate planning and financial resources are key to successful follow-up.

Environmental/Contextual vs. Individual-Level Risk Factors

Even though individual level risk factors in the context of drug use have been studied extensively, less is known about the environmental or contextual factors that influence risk. More recently researchers have begun to focus more attention on macro-level factors that may drive or add to individual-level risks. These factors may include social, economic, and even political issues. Although there is a large body of literature on this topic, this review will only briefly address the technical issues associated with studying drug users and not on the socio-political theoretical literature.

Previous research has shown that by focusing solely on reducing individual risk factors for injection drug use, only a partial decrease in transmission rates will result (165, 166). More recent work has focused on identifying group-level factors and how they interact with individual-level risk. For example, neighborhood factors such as employment rates, socioeconomic status, availability of specific injecting environments, and neighborhood characteristics have been associated with risk behavior (66, 165, 167-170). In addition, community activism also has been shown to be associated with public health policies. Research has shown the availability of needle exchange programs and drug treatment programs in certain areas may be based on political and social characteristics of the region (e.g., level of opposition/support of the community through the actions of grassroots organizations and budget priorities) (171, 172). However, contextual variables are difficult to measure and may not be handled sufficiently. For example, zip codes may be used as proxies for neighborhood, but may not accurately reflect the neighborhood unit that is most meaningful to residents, since this is an administrative boundary and may not represent residential location. In addition, findings from the Public Health Disparities Geocoding Project, undertaken to ascertain whether census or ZIP Code data would

be most apt for monitoring US socioeconomic inequalities in health, found mismatches between US-defined geographic areas and zip codes (173). Finally, studies of injection drug users often include homeless participants who do not have a fixed address.

Geographic information systems (GIS) are computer-based systems that analyze geographically referenced data. GIS has been described as "'automated systems for the capture, storage, retrieval, analysis and display of spatial data" (174). GIS technology can also be used to integrate social contextual factors into analyses, such as neighborhood characteristics (175). For example, in order to study social stressors, researchers may use information such as number of local bars, location of liquor stores, and drug corners. GIS allows for the inclusion of individual and environmental data to be viewed, analyzed and organized. GIS has been used to track the epidemiology of disease to identify trends(176). It has also been used to locate individuals at risk for disease to make decisions about prevention efforts (177). Recently, there has been an increased application of GIS to understand and study injection drug use. Trooskin et al. studied clustered HCV cases and identified areas of limited access to needle exchange, which suggested the need to expand the distribution of services (178). Brouwer et al. studied factors associated with injection drug use in the US/Mexico border city of Tijuana and subsequently developed tools to assist service providers and policy makers with information about how best to allocate spare resources (179). In particular, the GIS mapping helped to identify areas to be visited by the mobile health clinics. Although there are some limitations to the use of GIS, including the ability to distinguish the proportionate contribution of macro vs. individual level factors, the application of GIS in the study of injection drug use will improve the understanding of the interaction between individual and environmental risk factors for this at-risk population.

As the issues above indicate, it is extremely difficult to identify and study young, newly initiated injection drug users. Consequently, the limitations of studies of this population are to be expected given the obstacles to conducting reliable, valid and generalizable studies of such a marginalized population. However, with continuing efforts to design methodologies and strategies for studying this population, including the inclusion of internet and Smartphone surveys, investigators can improve access to these hidden populations, increase the efficiency and cost of conducting these important surveys, and ultimately make some headway in better understanding the risks faced and the prevention efforts required to reduce the burden of disease in young IDUs.

CHAPTER 2

Association between injection practices and duration of injection among newly initiated injection drug users

Abstract

Background: Earlier studies suggest higher infection risk among newly initiated injection drug users (IDUs) than more experienced users. Whether IDUs' risky injection practices rise progressively with duration of injection or frequency of practices is higher near initiation and then taper remains an open question.

Methods: Newly initiated IDUs were street recruited and interviewed between 1997 and 1999 as part of a multisite cohort study in five U.S. urban cities. Recent risky injection practices (injecting with others and injecting on average more now) were examined across three cross-sections defined by duration of injection: 0-1 year, 2-3 years, and 4-6 years.

Results: The IDU groups of <2 years duration (n= 691) and 2-3 years duration (n = 697) had higher odds than the 4-6 year group (n=520) of reporting injecting with others (Odds Ratio, OR = 1.52, and OR = 1.47, respectively) and injecting on average more now (OR = 1.44 and OR = 1.44, respectively). The associations remained after multivariate adjustment for demographic variables.

Conclusions: These data on newly initiated IDUs suggest that risky injection practices were more frequent earlier than later within the first 6 years of initiation, emphasizing that outreach and prevention needs to identify and intervene with IDUs early.

Introduction

Injection drug users (IDUs) are at high risk for a number of blood-borne infections, including HIV and hepatitis viral infections (180-182). Some data suggest a direct and proportionate increase in infection prevalence with duration of injection (183-185). This observation suggests on average a progressive course of injection drug use whereby the user experiences successive transitions from casual experimentation to dependence. This progressive transition in drug use may be due to incremental increases in dosage to offset tolerance and withdrawal. Also, as users transition from recreational to habitual, addictive use, they may prepare the drug less carefully and may share equipment, which, in turn, may result in syringes tinged with the blood of another person – the basis of transmission (186). However, other studies have shown that the risk of infection is higher soon after initiation of injection and stabilizes thereafter (183, 187). For example, Garfein and coworkers noted that the rates for hepatitis B and C viruses rose precipitously within the first two years following initiation of injection (188). Higher rates of HIV seroconversion among IDUs within two years of initiation than among those who had been injecting longer than two years have also been reported (189-191). These data suggest that IDUs may be more likely to engage in higher risk practices in the early stages of their injection career than during later stages. While these earlier studies were based on infection rates, and other studies have shown that infections are due to certain risk behaviors (192-194), data on the frequency of risk behaviors during these early years of injection drug use are sparse (180). Using data on IDUs who initiated injection within the prior 6 years, the primary purpose of this analysis was to determine whether certain recent behaviors (i.e., sharing equipment and injection frequency) known to confer risk of HIV and HCV infection transmission were more common

among IDUs within the first three years of initiation or for those who injected for greater than 3 years (the cut point defined a priori by half of the interval of 6 years that defined the sampling frame). The 6-year duration was selected a priori to be consistent with the sample definitions in earlier studies where infection risk in those who injected for 4-6 years approximated the rest of the cohort of IDUs that had an injection duration of a median of 13 years (range 7-40 years) (183).

Using data from a multicenter study among young and newly initiated IDUs, we performed this secondary analysis as hypothesis generation to distinguish whether the frequency of some injection practices started low and progressed to higher levels or were initially higher during this early period followed by a tapering off of frequency for these practices. Specifying the period of increased risk would help to refine our knowledge about injection practices among IDUs and provide additional information to consider when developing risk reduction programs. Higher frequencies of risk behaviors early in the injection career might embolden outreach efforts to new initiates into injection and even to non-injection drug users to prevent transition into injection, whereas a more gradual slope of lower to higher levels of risk behaviors over time might suggest that the window of prevention is wider.

Methods

Design and Study Population

The study population was recruited between 1997-1999 as part of the Collaborative Injection Drug Users Study (CIDUS-II), a multisite cohort study funded by the Centers for Disease

Control and Prevention (CDC) to identify risk of bloodborne infections among young, newly initiated IDUs. The study was conducted at 6 sites in 5 U.S. urban areas: Baltimore, Chicago, Los Angeles, New Orleans, and New York City (Harlem and the Lower East Side). A uniform protocol was developed across all sites for recruitment, eligibility, and assessment. Participants provided informed consent prior to study enrollment, interview, and venipuncture. The study received approval from the CDC and the institutional review boards at each of the participating sites.

Community-based outreach methods were used to recruit participants. Ethnographic mapping was undertaken to focus recruitment in places where young IDUs could be found. Recruitment involved street outreach by trained staff, flyer distribution, newspaper advertisements to identify index recruits followed by respondent-driven referral techniques (195). Recruitment efforts initially were focused on enrolling young (15-30 year old) or newly initiated IDUs (individuals injecting for 6 years or less), although the achieved samples were extended to include those who were up to 40 years old, and among those under 30 years old, an unspecified duration of injection. In order to focus on newly initiated IDUs, we restricted this analysis to those with duration of 6 years or less. While the overall study recruited 2435 participants, we excluded 597 participants because that reported injecting for more than 6 years. Two additional participants were excluded because of missing information on duration of injection.

Eligibility criteria included having begun to inject illicit psychoactive drugs for the first time within 6 years of enrollment and having injected at least once in the past 6 months. Injection status was verified by the presence of injection stigmata such as scars and abscesses or via a

series of questions designed to assess the plausibility of an individual's experience injecting drugs since newer injectors often have little evidence of injection use. Exclusion criteria were inability to provide informed consent and younger than 15 years of age or older than 30 years of age.

Data Collection

Eligible and consenting participants underwent standardized face-to-face interviews that lasted about 1 to 1 1/2 hours. The interview included information on sociodemographics, alcohol and drug use, injection practices, sexual behaviors, and institutionalization (i.e., spent time in a correctional facility, jail, juvenile detention center, prison, mental health ward of a hospital or mental health facility). Sociodemographic questions included site of recruitment, marital status, and history of homelessness. Injection practice questions focused on the recent history of frequency, duration, and location of drug use, and the sharing of equipment including cotton, cookers, and rinse water. Sexual behavior questions included condom use, giving and receiving drugs or money for sex, and whether partners used injection drugs.

Statistical Analysis

We calculated duration of injection from age of first injection to age at interview. Previous reports have noted that the date of initiation of injection is vividly recalled (180). In addition, both age of first injection and date of first injection (month and year) were asked of each injector, and the concordance was high (Kappa = 0.76). These approaches for determination of injection drug use duration are consistent with other studies (183, 185, 196). This definition presumes

consistent use throughout the period, which is supported by the eligibility criteria of being active within the 6 months prior to enrollment.

With a previously defined 6-year time frame (180, 183), we examined intervals in two ways. First, we divided the 6 years into 2 groups to capture up to 3 years versus more years. Second, we considered refinements such as whether responses by duration of injection might be linear (accelerate then decelerate frequency) or even non linear (e.g., inverted U-shape). Continuous measures were considered, but abandoned since the absence of this strategy in the extant literature would make results more difficult to interpret and compare. Therefore, we a priori established 3 categories that roughly divided the sample into tertiles by duration but maintained years as whole numbers: 0 to 1 years, 2 to 3 years, and 4 to 6 years. Among the 1836 participants included in the analysis, 34 % (n = 619) had been injecting for 0 to 1 years, 38 % (n = 697) for 2 to 3 years, and 28 % (n = 520) for 4 to 6 years.

We performed frequency distributions of select demographic characteristics, injection practices, and sexual behaviors stratified by the three groups to look at the proportion of participants in each sequential cross-section by these specified factors. We calculated unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) to examine the odds of engaging in select injection practices and sexual behaviors by duration of injection. For outcome variables, we a priori identified two injection practices. The first was injecting with others the last time you injected (“inject with others”), as this would indicate recent risk behavior. Second, we asked about injecting on average more now than 6 months ago (‘inject more now”), as this would indicate a trajectory of increasing drug use over time (reflecting higher tolerance and also increasing risk).

Since other studies have suggested that asking directly about needle sharing behaviors could be subject to socially desirable responding (197), we considered these variables to be proxies of sharing equipment and injection frequency, respectively and representative of the study participants' most recent behaviors. Secondary analyses included examining injection practices and sexual behaviors in the last 6 months to determine the relationship between these factors and duration of injection.

Outcome variables were dichotomized as half the time or less versus more than half the time. Studies of IDUs, including this one, tend to use scales for quantifying risk behaviors that include the two responses "never" and "always," reflecting never engaging in a behavior and thus absence of risk, or alternatively, always engaging in a behavior and thus the presence of risk, respectively, as well as several intermediate categories. We were concerned that restriction to extremes would result in small cell sizes and insufficient power, and the majority of the responses would fall within the intermediate categories. Therefore, a priori we created categories to distinguish if there were differences in frequency of practices in gross terms – engaging in a practice quite regularly (more than half the time) versus not regularly engaging in these activities (half the time or less).

To account for variation in demographic distributions between cross-sections defined by duration of IDU, we performed multivariate logistic regressions to estimate adjusted associations between duration of injection and the primary outcomes of interest (inject with others and inject more now). We also present saturated models with all demographic variables included. We selected variables based on prior knowledge and credibility given the available information regarding the

relationship between certain sociodemographic factors and injection drug use (198). Since the outcomes of interest were risk behaviors, we did not control for other risk behaviors in the multivariate models because of the high correlation between these behaviors. We also performed multivariate logistic regression to determine associations between duration of injection and risky behaviors (injection practices and sexual behaviors independently) in the last 6 months adjusted for demographic variables only since previous research has shown that injection practices and sex risk behaviors are highly correlated (199). Finally, we considered interaction terms to investigate whether associations between the primary outcomes of interest (inject with others and inject more now) and duration of injection differed by site of recruitment.

Results

Participants (n = 1836) in the three groups of IDUs (0-1 year, n =619; 2-3 years, n = 697; and 4-6 years, n = 520) differed in terms of mean age, gender, race, site of recruitment, marital status, homelessness in the last 6 months, initiated injection at <18 years of age, and initiated by someone > 5 years older (Table 1). They were similar in terms of the proportion that were institutionalized in the last 6 months, institutionalized ever, and had graduated high school or equivalent.

Table 2 shows the relationship between the recent practices (injects with others and injects more now) and duration of injection. The prevalence of newly injecting with others and injecting more now than 6 months ago were both significantly higher for IDUs of 0-1 year and 2-3 years than IDUs of 4-6 years. To determine whether there was a true relationship between injects

more now and duration of injection, we conducted an analysis of a sub-group of IDUs from 0-1 year (n = 343); IDUs of 6 months or less were excluded (n = 276). In this analysis, exclusion of these participants was done because by definition they were not injecting 6 months ago and would clearly be injecting more now than at that time. The relationship between duration of injection and injecting more now persisted for IDUs of more than 6 months to 1 year (OR = 1.51, 95% CI = 1.13-2.02).

After adjusting for certain demographic variables (age, sex, race/ethnicity, site of recruitment, marital status, homelessness in the last 6 months, initiated injection at < 18 years of age, and initiated by someone > 5 years), the adjusted ORs for injecting with others by duration of injection were not significantly altered (Table 2). The higher-level risky injection practices in the earlier years persisted. After adjusting for the demographic variables, the associations between inject more now and duration of injection persisted for IDUs of 2-3 years as compared to IDUs of 4-6 years. We found no significant interaction between site of recruitment and duration of injection with respect to the primary outcomes of interest, inject with others and inject more now (data not presented).

Table 2 also presents adjusted ORs (and 95% CI) for injection practices over the last 6 months and duration of injection. After adjusting for demographic factors, backloading became significantly different for IDUs of 2-3 years compared with IDUs of 4-6 years, a relationship that was not significant in univariate analysis. The adjusted ORs for injection practices of sharing cookers and cotton and sharing rinse water by duration of injection were not significantly changed -- IDUs of 2-3 years had higher odds of sharing cookers and cotton and sharing rinse

water. The relationship between the lack of certain safer practices such as used a new needle and duration of injection did not hold for the 0-1 year group as compared to the 4-6 year group after adjustment for demographic variables; however, it did hold for IDUs of 2-3 years. It also persisted for the relationship between the lack of other safer practices such as the use of new needles from NEP – IDUs of 0-1 year and 2-3 years had lower odds than IDUs of 4-6 years of using new needles from the NEP.

We also analyzed the associations of selected sexual practices by duration of injection for the last 6 months (data not shown). We analyzed, separately for men and women, the odds of having partners who inject and found the odds to be significantly lower for IDUs of 0-1 year than IDUs of 4-6 years for both sexes (men: OR = 0.72, 95% CI = 0.52-0.99; women: 0.63, 95% CI = 0.43-0.94). This relationship between having a partner who injects drugs and duration of injection (0-1 year vs. 4-6 years) persisted after adjusting for demographic variables (OR = 0.69, 95% CI = 0.54-0.88). We found no significant difference between IDUs of 2-3 years and 4-6 years (men: OR = 0.87, 95% CI = 0.64-1.17; women: OR = 0.87, 95% CI = 0.58-1.28). We detected no difference between men and women in the three duration groups in terms of the odds of such practices as giving or receiving drugs or money for sex or using a condom with both steady and casual sexual partners (data not shown).

Discussion

The major finding of this study was that frequency of risky injection practices appears to be higher in the most newly initiated IDUs. Beyond the two hypothesized recent injection practices,

we found that the frequency of some other injection practices such as indirect sharing (sharing of cookers and cotton and sharing of rinse water) and backloading were also higher. The frequency of preventive behaviors was lower in the most recent onset IDUs. These observations further support the studies showing that newly initiated IDUs risk of infection is higher in earlier years of an injection career, and these data provide some evidence to suggest that within the first 6 years, the pattern is likely to be initially higher risk that tends to taper off rather than a monotonic increase in risky behaviors.

When we examined sex practices in our sample, the patterns of sexual risk were less clear. While the proportion having an IDU sex partner was lower for recent initiates of 0-1 year and 2-3 years than IDUs of 4-6 years, we did not observe a relationship between duration and risky sexual practices such as giving or receiving drugs or money for sex or frequency of condom with either steady or casual sexual partners. The fewer IDU partners probably reflect network composition evolving with injection experience. While recent articles (200, 201) have shown that IDUs have substantial sexual risks for acquisition of infections, their findings were based on more experienced cohorts while ours was restricted to more newly initiated IDUs. Additional studies to clarify these observations are needed.

Several study limitations should be acknowledged. First, although we stratified by duration of IDU and adjusted for demographic factors, the data come from a cross-section, which has well known limitations. For example, the use of sequential cross-sections does not account for individual changes over time, and differences observed can reflect the different people recruited. More broadly, without a sampling frame, the generalizability to other IDUs, even within the

participating cities, remains unknown. In terms of another factor related to sampling, we are sensitive to the possibility that more risky IDUs might have been less likely to survive and populate the longer duration subsamples. Given the narrow exposure time of our study participants (less than 6 years of injection drug use), survivor bias is probably less of a significant concern; however, future studies should include a prospective follow-up to clarify the findings of this study.

The issue of validity of self-reports is a topic that arises frequently in studies of sensitive behaviors in hidden populations. However, reviews of this topic for drug users show high levels of reliability and validity outside of treatment settings (197). Participants were asked to describe behaviors during the prior 6 months. This averaging over an interval assumes that behaviors are constant and without dramatic changes during this period. Thus, the data here might not capture the nuances of variation in levels of risky practices. However, an earlier study that compared responses for the past month and the past 6 months showed that dividing the 6-month responses by 6 achieved the same results in 85% of the participants (202).

With limitations acknowledged, this study provides information about the frequency of risk by duration of injection drug use among those who have injected for 6 years or less. Our findings provide complementary information for the observations made by others about the higher infection rates in earlier years of the injection career (183, 189, 191, 203). The fact that some risks were immediate and others partially delayed helps us to better understand that the story of risk is complex. The richness and complexity of the data indicate that there are multiple opportunities to insert prevention messages.

Given the period of increased risk is early in the injection career, outreach efforts should focus on new initiates into injection drug use. Newly initiated IDUs need to be educated to practice safer techniques in order to reduce the incidence of HIV and other blood-borne infections. IDUs may not openly identify themselves as such, and they may be less likely to seek out health care and drug treatment programs. Young or newly initiated IDUs in particular may be especially unwilling to utilize such services. For this reason, newly initiated IDUs may be more difficult to identify for prevention efforts. Particular attention should be paid to locating these subjects and providing them with appropriate prevention programs. An alternative is to recognize that high risk occurs sufficiently early and that prevention may also need to be geared to the subset of non-injection drug users at risk for transition into injection (204).

In summary, studies like the one reported here aim to improve understanding about the periods of increased risk that can help to refine the knowledge about injection practices among IDUs and provide additional information to consider when developing risk reduction programs**.**

Table 1. Baseline sociodemographic variables by duration of injection

	0-1 Yr. (N = 619)	2-3 Yrs. (N = 697)	4-6 Yrs. (N = 520)	P-value*
Age, mean (std dev)	22.9 (4.5)	22.9 (4.3)	23.7 (4.0)	0.001†
Male, % (n)	56 (344)	62 (432)	62 (324)	0.024
Race, % (n)				
White	52 (322)	54 (374)	59(306)	
Black	22 (137)	22 (154)	17 (90)	
Hispanic	20 (121)	15 (107)	17 (86)	0.034
Other	6 (38)	9 (62)	7 (520)	
Site of recruitment, % (n)				
Baltimore	14 (89)	16 (109)	10 (53)	
Chicago	44 (271)	34 (237)	21 (109)	
Los Angeles	13 (82)	15 (104)	22 (115)	
New Orleans	7 (46)	12 (84)	11 (58)	
New York - Harlem	6 (39)	8 (52)	9 (45)	< 0.001
New York - Lower East Side	15 (92)	16 (111)	27 (140)	
Single/Never Married, % (n)	88 (545)	89 (621)	83 (433)	0.008
Homeless - last 6 months, % (n)	39 (241)	48 (332)	57 (294)	< 0.001
Institution – last 6 months, % (n)	47 (235)	44 (245)	44 (176)	0.488
Institution – ever, % (n)	81 (498)	79 (553)	78 (405)	0.567
High School Grad. or GED, % (n)	51 (314)	51 (352)	53 (273)	0.763

* Chi-square statistic
† ANOVA, F statistic

Table 2. Frequency distributions, odds ratios (ORs) and adjusted ORs for selected injection practices by duration of injection

Injection Practices	0-1 Yr. % (N= 619)	0-1 Yr. OR* (95%CI)	0-1 Yr. Adjusted OR*† (95% CI)	2-3 Yrs. % (N = 697)	2-3 Yrs. OR* (95% CI)	2-3 Yrs. Adjusted OR*† (95% CI)	4-6 Yrs. % (N = 520)
Recent							
Inject with others last time injected	66%	1.52 (1.20-1.94)	1.61 (1.24-2.09)	65%	1.47 (1.17-1.86)	1.54 (1.20-1.98)	56%
Inject on average more now than in the last 6 month	36%	1.44 (1.12-1.86)	1.26 (0.97-1.64)	36%	1.44 (1.13-1.83)	1.34 (1.04-1.71)	28%
Past 6 month							
Needle sharing - follow someone (more than half the time)	7%	1.27 (0.79-2.03)	1.14 (0.70-1.86)	8%	1.27 (0.80-2.01)	1.25 (0.78-2.00)	6%
Backloading (more than half the time)	7%	1.55 (0.94-2.57)	1.90 (1.12-3.23)	6%	1.27 (0.76-2.11)	1.44 (0.85-2.44)	5%
Indirect sharing -cookers/cotton (more than half the time)	27%	1.24 (0.94-1.62)	1.24 (0.93-1.64)	31%	1.49 (1.15-1.94)	1.53 (1.17-2.01)	23%
Indirect sharing – rinse water (more than half the time)	20%	1.19 (0.88-1.61)	1.10 (0.80-1.50)	25%	1.54 (1.18-2.09)	1.57 (1.17-2.10)	17 %
Used a new needle (half the time or less)	53%	1.32 (1.04-1.67)	1.22 (0.95-1.54)	57%	1.50 (1.19-1.89)	1.47 (1.16-1.85)	46%
New needles from NEP (half the time or less)	72%	1.92 (1.52-2.50)	1.52 (1.18-1.96)	70%	1.82 (1.43-2.33)	1.56 (1.22-2.00)	57%

Used bleach on a used needle (half the time or less)	83%	0.83 (0.61-1.15)	0.88 (0.63-1.22)	82%	0.78 (0.57-1.06)	0.80 (0.59-1.10)	85%
IDU everyday (≥ everyday v. all others)	36%	0.89 (0.69-1.12)	0.78 (0.61-1.00)	46%	1.14 (0.90-1.43)	1.21 (0.96-1.54)	43%

Note: OR = odds ratio; CI = confidence interval

* Reference group: IDUs of 4-6 year

† Adjusted for age (continuous variable), sex, site of recruitment, race/ethnicity (white, black, Hispanic, other), homeless in the last 6 months (yes/no), single/never married (yes/no)

CHAPTER 3

Racial differences by duration of injection in prevalence of Hepatitis C virus among young, newly initiated injection drug users

Abstract

Background: The association between blood-borne infections and duration of injection and race/ethnicity continues to be an open question given the discrepant finds of earlier studies.

Methods: Injection drug users (IDUs) were street-recruited in 6 U.S. urban areas from 1997 to 1999. Prevalence of Hepatitis C virus (HCV) was examined by duration of injection (0-1 year, 2-3 years, and 4-6 years) among individuals who injected for 6 years or less as well as by race/ethnicity and site of recruitment.

Results: Overall HCV prevalence was 34%. By duration of injection, HCV prevalence in Baltimore for blacks increased from 33.3% among IDUs injecting <2 years to 79% among IDUs injecting 4-6 years. HCV prevalence in other cities (Chicago, Los Angeles, New Orleans and New York) showed less difference by duration. By racial and ethnic group, HCV prevalence was higher in blacks than non-blacks (=80% white) in all cities (OR = 1.43, 95% CI: 1.00 – 2.05) except Baltimore where prevalence was higher in whites (OR = 5.20, 95% CI: 2.94 – 9.18) than blacks (OR = 2.52, 95% CI: 1.38 – 3.07) as compared to whites in all other cities.

Conclusions: These data from a multicenter study with standardized data collection suggest a pattern of HCV by duration of injection and racial/ethnic group whereby HCV prevalence while higher in blacks than whites as in most previous studies, the reverse in Baltimore for IDUs < 4 -6 years was present and merits additional attention.

Introduction

Hepatitis C virus (HCV) remains an important public health problem, and injection drug use continues to be one of the primary risk factors for infection through the sharing of needles and drug-preparation equipment (1).

Earlier studies that have examined rates of infection by duration of injection have found HCV prevalence rose alarmingly within the first two years of injection, indicating that the initial period of injection constituted higher risk than later periods (> 2 years) (21). Others contended that there was a more gradual increase by duration of injection drug use (18, 124, 205, 206). Inconsistencies in HCV prevalence by duration of injection seen across studies may be due to a variety of factors including differences in recruitment methods or calendar time between studies. The second Collaborative Injection Drug Users Study (CIDUS-II), a multisite study conducted with a uniform design and recruitment method during a discrete calendar period, can contribute to this ongoing dialogue. Results from this analysis may have implications for further refining prevention strategies during this short window of opportunity for intervention after initiation of injection drug use.

Methods

Data from CIDUS-II were used for the analysis. Methods from this study have been described in detail elsewhere (22, 207). In brief, the CIDUS-II study was a multisite study funded by the Centers for Disease Control (CDC) to study young, injection drug users (IDUs). The study

population was recruited from 1997 through 1999 at six sites (Baltimore, MD; Chicago, IL; Los Angeles, CA; New Orleans, AL; New York City –Harlem, NY; and New York City – Lower East Side, NY), using community-based convenience sampling methods. A uniform protocol was followed for recruitment, eligibility assessment, interviewing procedures and serum collection. Informed consent was obtained prior to study enrollment, interview and venipuncture. The study received CDC approval as well as institutional review board approval at each of the study sites.

While the overall study recruited 2435 participants, in order to focus on young (18-30 years) and newly initiated ($\leq$ 6 years) IDUs, 710 participants were excluded for this analysis (597 reported injecting for more than 6 years, 111 were outside the age restriction of $\geq$ 18 years and $\leq$ 30 years, and 2 were missing information on duration of injection drug use).

Blood specimens were sent to the CDC for serologic testing for HCV antibodies (Abbott HCV enzyme immunoassay 2.0; Abbott Laboratories, Chicago, Illinois). All positive samples were retested by enzyme-linked immunosorbent assay, but confirmatory testing was not performed on baseline samples because of the high positive predictive value of repeat reactive enzyme immunoassay testing in this population when samples are tested against a confirmatory assay (A sample of 100 specimens repeatedly reactive for HCV based on EIA received supplemental testing and were all found to be positive) (208).

Duration of injection was calculated from self-reported date of initiation of injection drug use to date of baseline interview. Intervals of duration were divided into three categories (0-1 year, 2-3

years, and 4-6 years), which separated the participants into approximately equal groups, while maintaining years as whole numbers. Frequency distributions of select sociodemographic variables by duration of injection were calculated and compared using a chi-square test to compare the differences for categorical variables and one-way ANOVA for continuous variables. Based on prior information regarding the relationship between certain demographic factors, injection practices and disease prevalence, unadjusted odds ratios (ORs) and 95 % CI were calculated between HCV prevalence and duration of injection, race, site of recruitment, and select demographic and injection behaviors. All statistically significant factors ($p< 0.05$) were considered in the multivariate logistic regression models. Interaction terms were evaluated for statistical significance based on their biologic plausibility, and statistically significant interaction terms were included.

Results

Among the 1725 participants included in this analysis, mean age was 23 years, and more than half were male (60%) and white (54%); 21% of the participants were black. As Table 1 shows, site specific differences included age, sex, race, site of recruitment, marital status, homelessness in the last 6 months, initiation of injection at < 18 years of age, and initiation by someone > 5 years older.

Overall HCV prevalence was 34%. HCV prevalence for the three groups was similar (33.9%, 36.3%, and 37.2% for IDUs of 0-1 year, 2 – 3 years, and 4-6 years, respectively). When HCV prevalence was further examined by site, significant differences emerged (Figure 1), with the

highest rise in prevalence by injection duration seen in Baltimore. In Baltimore HCV prevalence was 41% among the newest injectors (< 2 years), and rose to 78% among injectors with 4-6 years duration. When HCV prevalence was examined separately by injection duration and race/ethnicity (Figure 2a), blacks were more likely than other groups to be infected. The HCV prevalence among black injectors with 4-6 years since initiation was 54%.

Figure 2b shows that in Baltimore, HCV prevalence among blacks was 33.3% among the newest injectors (< 2 years) and was as high as 80% among injectors of 4 – 6 years since initiation. In Figure 2c, for non-blacks, HCV prevalence was higher for the newest injectors, with a prevalence of 59% for the newest injectors (< 2 years) and almost 77% among injectors of 4-6 years since initiation.

With two-thirds of study participants in Baltimore identified as black, we moved to disentangle whether the higher HCV prevalence in Baltimore might be related to racial/ethnic grouping vs. site of recruitment. Table 2 shows unadjusted ORs (and 95% CIs) for the association between prevalence and duration of injection, race and site of recruitment. It also includes adjusted ORs (and 95% CIs), adjusting for sociodemographic factors (age) and injection practices significant in bivariate analysis (i.e., initiated injection at < 18 years, initiated by someone > 5 years older, frequency of injection drug user and IDU partner). Injectors from Baltimore who were black were 2 times more likely than non blacks from other sites to be HCV positive. Injectors from Baltimore who were not black were 2.5 times more likely to be HCV positive than blacks from Baltimore and 5 times more likely to be HCV positive than non-blacks from other sites.

Discussion

Our results show patterns that have been demonstrated in previous studies –high rates soon after initiation in certain cities (Baltimore) as well as gradual increases in other locales (Chicago, Los Angeles, New Orleans and New York), indicating that there may be regional variability in the epidemic, and patterns are localized.

Of note, we observed a strikingly high prevalence of HCV infection soon after initiation among early injectors in Baltimore. Interestingly, this pattern was similar to those observed in Baltimore in the late 1980s (21). When we analyzed the data further to better understand the reason for Baltimore's more dramatic rise in HCV infection among young injectors to determine if it was related to race/ethnicity or was simply a local phenomenon, we found higher HCV prevalence in non-blacks than blacks in Baltimore in the newly initiated group. Nearly all previous studies that compare racial/ethnic groups have reported higher prevalence in blacks than whites, with only few reporting either no difference between whites and blacks or higher rates in whites than blacks (26, 209-211). In a meta-analysis by Hagan, blacks had a slightly higher HCV prevalence but it was not significant (OR = 1.34, 95% CI = 0.89 – 2.02) (3).

Although studies have shown that drug use is more prevalent in suburban, higher income communities than urban lower income ones, and white injection drug users are younger at initiation than blacks (122, 212), black injection drug users are more likely to be at risk of blood borne infections (213). Consequently neighborhood characteristics and social and economic context (e.g., more availability of drugs, higher unemployment rates, more social distress, etc)

may a play a role individual risk behaviors. Young, newly initiate IDUs have been shown to be more likely to report high risk networks (214).

These findings of high prevalence of HCV among newly initiated injectors in Baltimore are consistent with the surveillance data of Baltimore in the 1990s. Baltimore has been cited as the heroin capital of the US (215). According to the Office of National Drug Control Policy and the Drug Enforcement Agency, Baltimore was one of the leading heroin drug markers in the US in the 1990s (216). In the mid-1990s, Baltimore became a key East Coast distribution point for high purity South American heroin, which is substantially more potent than its East Asian and Mexican counterparts, making it more addictive and more deadly (216). The high levels of heroin purity found in Baltimore, as high as 94%, allowed for easier initiation for young people by intranasal route (217). Higher purity, increased availability and cheaper prices have helped to encourage new users within the US and globally (218).

Consequently, Baltimore is well above the national average of drug use and addiction. Since the 1990s, heroin use among 8th and 10th in Baltimore has been consistently higher than national averages (219). From treatment admission data, reported heroin use rose yearly from the late 1990s and early 2000s for people over the age of 18 (220, 221). In the Baltimore area, heroin accounted for over 60% of drug-related treatment admissions as compared to 28% in Chicago, 25% in Los Angeles , and 12% in New Orleans, three of the other study locations within this analysis (221). Fatal overdose rates in Baltimore increased by over 400% from 1990 to 1997, as compared to the national average of 57%. (222). The high prevalence of HCV seen in Baltimore

in this analysis as compared to the other study cities appears to reflect the trends in heroin use and abuse in Baltimore during the same period.

In our effort to weigh in on the discrepancy in the patterns by duration of injection noted in earlier reports (18, 21, 24, 157, 223), we did so with the advantage of our study design. Unlike most previous reports, ours came from a multicenter study conducted using similar methods and performed during the same two year period. A previous analysis of HCV prevalence by duration was conducted using the CIDUS-II data (19); however, the higher prevalence in whites in Baltimore has been previously unexplored.

The data have certain limitations. Participants differed at individual sites with respect to demographic, drug use and sexual behaviors. We adjusted for site differences, but may not have accounted for all confounding factors. Although prevalence by duration of injection is a proxy for incidence, with cross-sectional data we are making assumptions that the study participants constitute a cohort across the study period. Incidence data and longer-term follow-up of these new injectors would be preferred. Finally, this is not a randomly selected sample, so the extent to which these findings can be generalized to other populations, even other persons within the same cities is unknown.

With caveats acknowledged, our data confirm high prevalence of HCV early soon after initiation of injection across 6 sites in 5 U.S. cities at the end of the 1990s. In addition, increases in HCV prevalence by duration of injection differ across U.S. cities, with the unanticipated finding of whites with a higher prevalence of HCV infection than blacks in Baltimore to begin with, but

with Blacks rapidly catching up once they had been injecting for 6 years. With this increased risk during the early period for young, newly initiated IDUs, only a short window of opportunity to prevent infections within this population may be available. Understanding racial and regional differences may be important for developing prevention strategies more appropriately geared to the specific populations. Active monitoring of local epidemics is important, and outreach must begin quickly with greater efforts focusing on new initiates. In addition, particular attention should be paid to understanding the individual risk factors as well as social factors that may be the cause of the alarmingly high rates in Baltimore to better focus prevention efforts in that community as well as to avoid similarly explosive epidemics in other regions.

Table 1. Baseline sociodemographic variables by site of recruitment

	Site of Recruitment						
Variable	Baltimore n = 244 (14.1%)	New York - Lower East Side (NDRI) n = 306 (17.7%)	New York - Harlem (NYAM) n = 133, 7.7%	New Orleans n = 182, 10.6%	Los Angeles n = 257 (14.9%)	Chicago n = 603 (35%)	p-value*
Age, mean (SD)	25.2 (3.5)	22.3 (3.6)	24.9 (3.0)	21.3 (2.3)	21.9 (3.2)	23.1 (3.7)	< 0.001[a]
Male, % (n)	37.9% (92)	64.4% (197)	65.4% (87)	63.7% (116)	61.5% (158)	64.0% (386)	< 0.001
Race, % (*n*)							
White	28.7% (70)	76.1% (233)	13.5% (18)	45.6% (83)	65.4% (168)	60.2% (363)	
Black	67.2% (164)	3.6% (11)	9.0% (12)	44.0% (80)	3.9% (10)	14.4% (87)	
Hispanic	1.6% (4)	12.4% (38)	73.7% (98)	2.2% (4)	9.3% (24)	22.1% (133)	
Other	2.5% (6)	7.8% (24)	3.8% (5)	8.2% (15)	21.4% (55)	3.3% (20)	<0.001
Years of Injection Drug Use							
0-1 year	15.2% (87)	14.2% (81)	6.8% (39)	7.5% (43)	10.0% (57)	46.2% (264)	
2-3 years	16.2% (106)	15.3% (100)	7.6% (50)	12.4% (81)	13.3% (87)	35.2% (230)	
4-6 years	10.2% (51)	25.0% (125)	8.8% (44)	11.6% (58)	22.6% (113)	21.8% (109)	< 0.001

Single/never married, % (n)	84.8% (207)	90.5% (276)	69.9% (93)	92.9% (169)	92.2% (236)	86.9% (524)	<0.001
Homeless - last 6 months, % (n)	27.3% (66)	79.7% (243)	39.4% (52)	62.1% (113)	65.0% (167)	26.9% (162)	<0.001
Institution - last 6 months, % (n)	35.8% (67)	41.3% (88)	25.0% (29)	52.7% (87)	50.8% (99)	48.7% (239)	<0.001
Institution - ever, % (n)	76.6% (187)	69.9% (213)	87.2% (116)	91.2% (166)	75.9% (195)	81.4% (491)	<0.001
High school graduate or greater, % (n)	36.1% (88)	59.5% (182)	45.1% (60)	37.9% (69)	55.6% (143)	58.2% (351)	<0.001
Initiated injection < 18 years of age, % (n)	8.2% (20)	38.2% (117)	6.0% (8)	48.4% (88)	41.6% (107)	18.1% (109)	<0.001
Initiated by someone > 5 years older, % (n)	49.0% (98)	25.8% (64)	52.5% (53)	38.2% (55)	31.8% (69)	33.5% (169)	<0.001

* X^2 statistic

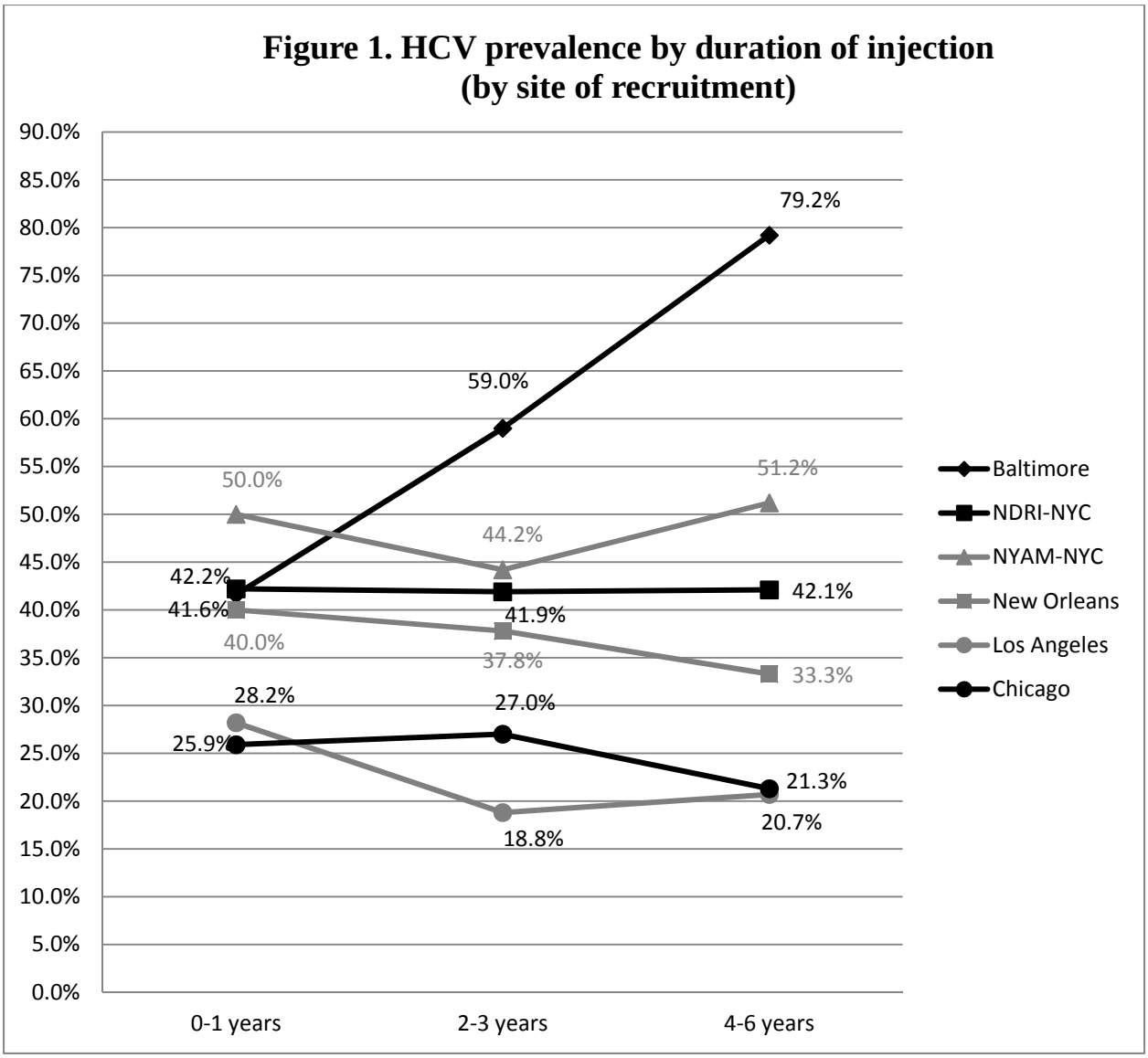
[a] ANOVA, *F* statistic

Table 2. Odds ratio (OR) and adjusted ORs for HCV prevalence for selected variables by duration of injection, race and site of recruitment

Variable	HCV (N = 588) OR (95% CI)	Adjusted OR (95% CI)*
Duration of injection		
0- 1 year	1.00	1.17 (0.90 - 1.52)
2-3 years	1.12 (0.88 – 1.42)	1.12 (0.84 – 1.48)
4-6 years	1.16 (0.89 – 1.50)	1.29 (0.93 – 1.78)
Race /Site		
Not Black/Not Baltimore†	1.00	1.00
Black/Not Baltimore†	1.67 (1.23 – 2.27)	1.43 (1.00 – 2.05)
Black/Baltimore	2.30 (1.65 – 3.21)	2.06 (1.38 – 3.07)
Not Black/Baltimore	5.21 (3.17 – 8.55)	5.20 (2.94 – 9.18)

*Adjusted for age, initiated injection at < 18 years, initiated by someone > 5 years older, frequency of injection drug use, and IDU partner. Not included in multivariate model because non-significant in the bivariate analysis: sex, marital status, and homeless.

† Not Baltimore: Chicago, Los Angeles, New Orleans, New York – Harlem (NYAM), and New York – Lower East Side (NDRI)



* New York City – Harlem (NYAM - NYC), and New York City – Lower East Side (NDRI - NYC)

HCV Prevalence	0-1 years	2-3 years	4-6 years
Baltimore	41.6%	59.0%	79.2%
NDRI-NYC	42.2%	41.9%	42.1%
NYAM-NYC	50.0%	44.2%	51.2%
New Orleans	40.0%	37.8%	33.3%
Los Angeles	28.2%	18.8%	20.7%
Chicago	25.9%	27.0%	21.3%

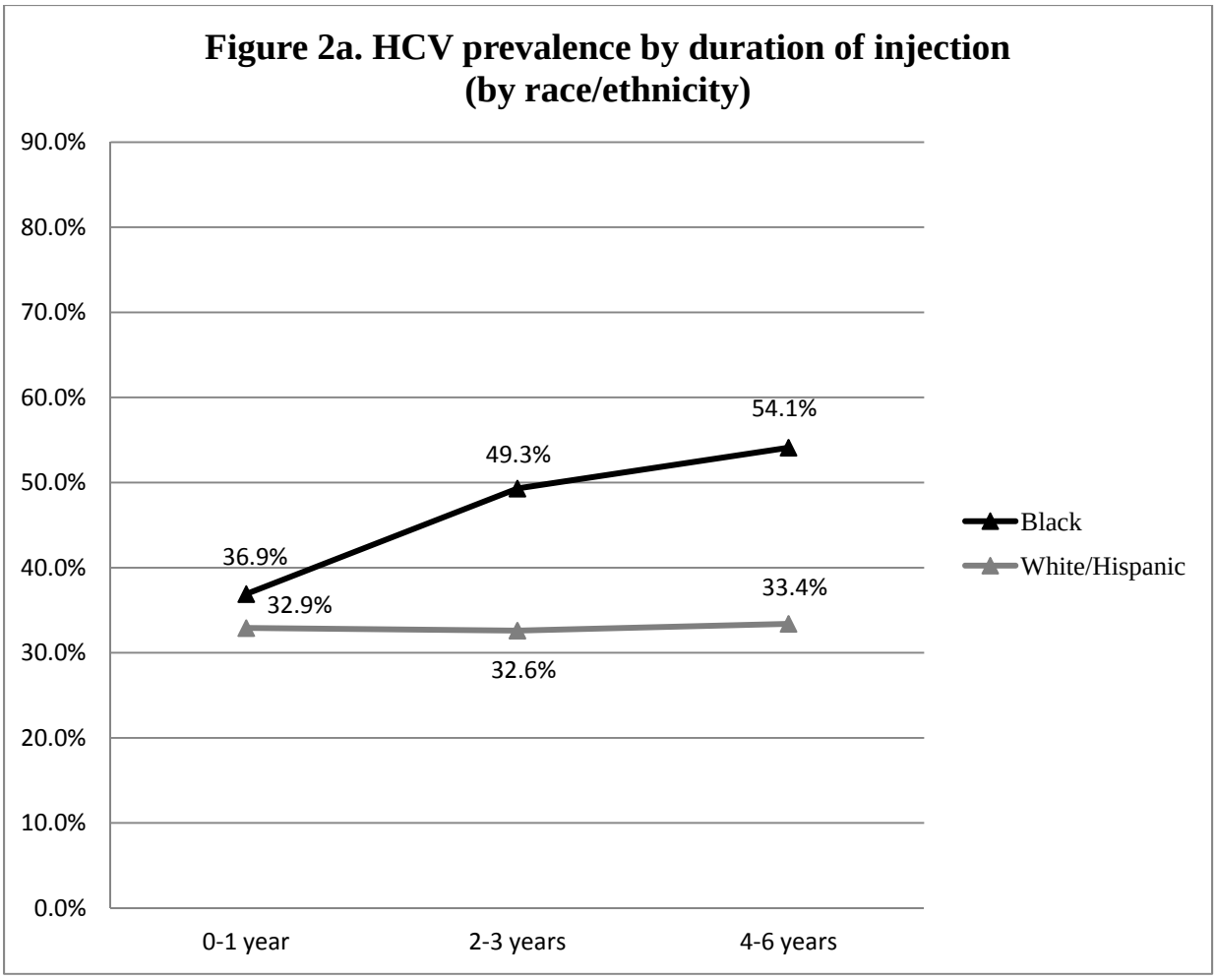
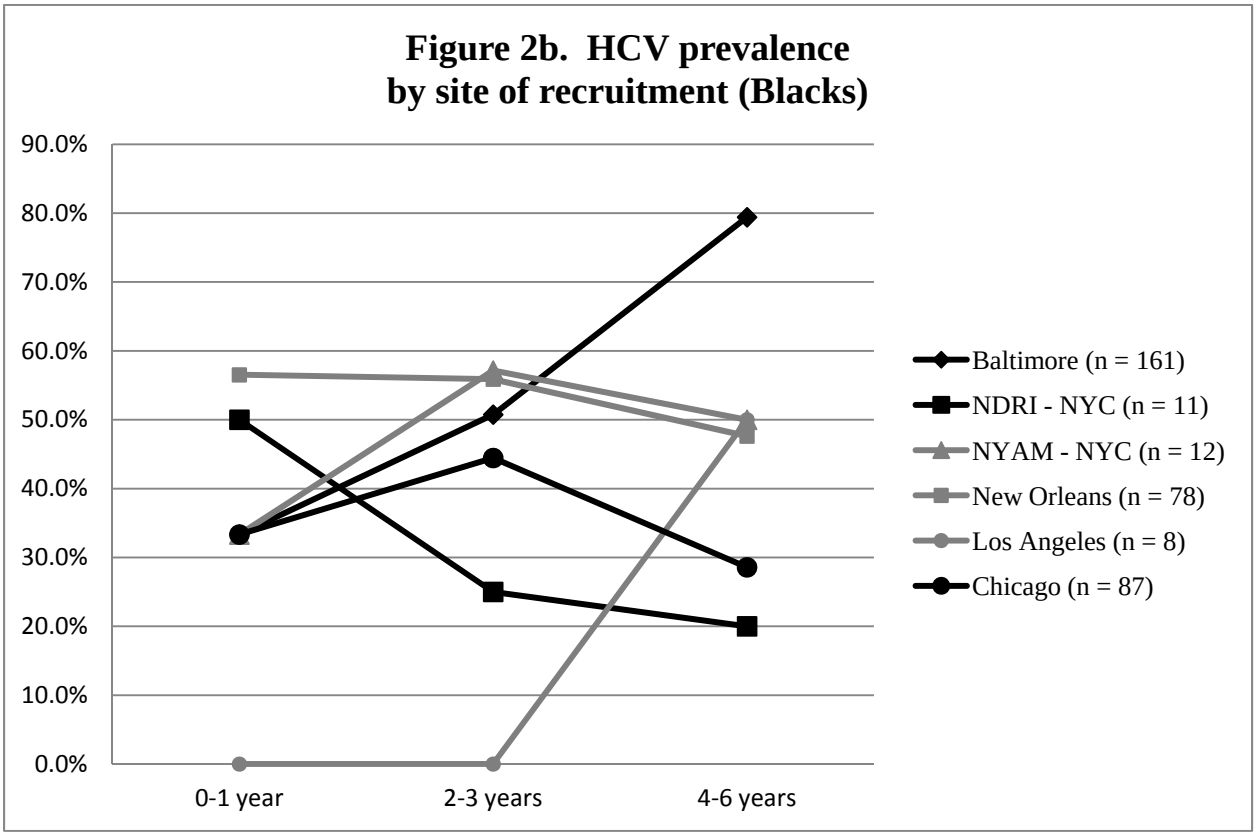
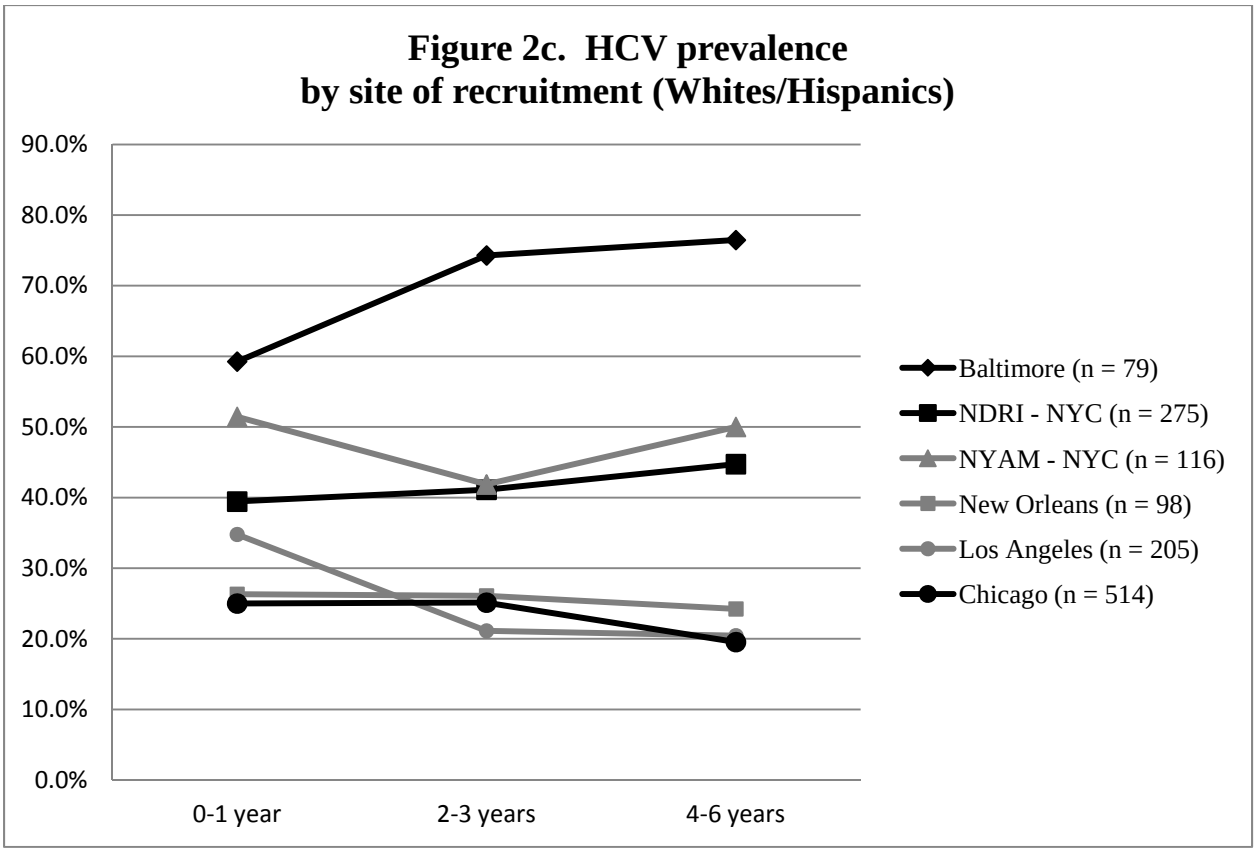


Figure 2a. HCV prevalence by duration of injection (by race/ethnicity)
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
0-1 year
2-3 years
4-6 years
36.9%
49.3%
54.1%
32.9%
32.6%
33.4%
Black
White/Hispanic



* New York City – Harlem (NYAM - NYC), and New York City – Lower East Side (NDRI - NYC)



* New York City – Harlem (NYAM - NYC), and New York City – Lower East Side (NDRI - NYC)

CONCLUSIONS

The aim of this research was to improve understanding of the certain baseline characteristics and risk behaviors by duration of injection drug use, focusing on the early period after initiation into injection drug use. While some studies looking at prevalent and incident HIV and other blood borne infections such as Hepatitis C (HCV) have shown a proportionate and direct increase with duration of injection drug use, a number of other studies have suggested that the risk of infection is higher immediately following initiation. The discrepancies in patterns shown in previous studies may be due to the lack of comparability across studies with regard to recruitment methods or the calendar time when the study was conducted. This study used a uniform design across several study sites during a specific calendar period to provide additional insight to the ongoing dialogue.

The frequency of several important risky injection practices were found to be higher among more newly initiated IDUs, including frequency of injection, injecting with others, indirect sharing (sharing of cookers, cotton and rinse water) and backloading. In addition, the frequency of certain preventive behaviors was found to be lower among this group as well, including use of new needles and NEPs. The analysis of risky sexual practices by duration of injection resulted in less consistent findings. The frequency of having an injection drug using partner was lower for more newly initiated IDUs, AND there did not appear to be an association between duration of injection and sexual behaviors such as giving or receiving sex for money or drugs or use of condoms with sexual partners. These data support findings of a period of increased risk early in the injection career.

Additional analyses were conducted using HCV prevalence data to examine the association between HCV prevalence and duration of injection by certain baseline characteristics (i.e., race/ethnicity and site of recruitment). The analysis showed that HCV prevalence was high after initiation of injection in certain cities (Baltimore), whereas a more gradual increase was observed in other cities (Chicago, Los Angeles, New Orleans and New York). Interestingly, prevalence of HCV among newly initiated injectors (<4 years) was higher for non non-blacks than blacks in Baltimore. These results further refine the findings regarding risky behaviors among young, newly initiated injection drug users and indicate that there may be regional variability in the epidemic as well.

Limitations

These data have certain limitations. First, there are limitations to using sequential cross-sections to mimic longitudinal changes in behavior. Changes in behavior may not be the result of length of injection, but rather variations in the subject's selected. Longer-term follow-up of these new injectors would be preferred.

Participants differed at individual sites with respect to demographic, drug use and sexual behaviors. Adjustments for site differences were made, but may not have addressed all confounding factors.

In addition, the results of this study may not be generalizable to other injection drug users and more specifically young, newly initiated injection drug users, given the lack of sampling frame.

In addition, risky drug users may not have survived to be included in the cohort of longer term users in this analysis. However, the narrow time frame of this study population (6 years or less of injection drug use) makes the issue of survivor bias less consequential in this analysis.

Finally, the reliability and validity of self-reported data are of concern when studying sensitive issues. However, outside the treatment setting, there is a perceived level of confidentiality and privacy, and self-reports are considered to provide adequately valid information about drug use and other risk-taking behaviors.

Strengths of this Study/Public Health Impact

HIV and other blood borne infections are serious diseases that are critical disruptions in our society. This study addressed an important public health issue –injection drug use, which continues to be one of the major risk factors for the acquisition of HIV. Previous studies have shown a link between risk of infection and certain behaviors. Young, newly initiated IDUs, who are often difficult to locate and recruit for studies, merit additional attention. These studies have found that risk of infection is higher in more newly initiated IDUs as compared to more experienced drug users. These data support additional evidence that young, newly initiated injection drug users behave differently than older, longer-term users. Additional research has shown that younger, more newly initiated IDUs may have less knowledge of HIV and risk of acquisition and may be less likely to identify as an IDU (28).

Better understanding of risk behaviors among younger IDUs is warranted in order to better understand trends in HIV and HCV risk and devise appropriate prevention efforts. Particular effort should be paid to locating these subjects, and providing them with appropriate prevention programs. Efforts to prevent the HIV and other bloodborne infections among IDUs must include harm reduction efforts such as drug treatment programs, needle exchange programs, street outreach, and counseling and testing, which all have shown benefit for reducing injection drug use and the risk of HIV and other blood borne infections (224, 225).

However, IDUs may not openly identify themselves as such, and they may be less likely to seek out health care, drug treatment programs and other services. Young, newly initiated IDUs in particular may be unwilling to utilize such services, and more marginalized groups such as homeless or ethnic minorities, pose additional challenges. Consequently, efforts to prevent HIV and other bloodborne infections among IDUs must include efforts to include education and outreach among younger, more newly initiated IDUs. For example, young, newly initiated IDUs may not want to associate themselves with other injection drug users and identify themselves as one. They may not consider their drug use as habitual, but rather consider themselves more of an experimenter, so they may not be ready to make their drug use public. Participating in needle exchange programs would require presenting themselves as an IDU to the program staff. The use of vending machines and mobile van exchange programs for needle exchange allow for more anonymous access and limited opportunity to be identified, and thus may be more appealing to young, newly initiated IDUs. One study in France found that use of vending machines were more common for younger IDUs and an effective and cost-effective option to more traditional needle exchange efforts (226). Additional studies have shown the benefit of vending machines

and mobile vans as methods for accessing harder-to-reach and higher risk individuals (227). In addition, studies have shown that involving peers (e.g., street youths) in outreach may make more newly initiated injectors more willing to self-identify and engage in prevention efforts (225).

By the time injection drug users often access drug treatment programs or needle exchange programs, they may already be infected. Additional efforts should be made to reach these individuals earlier. Information about initiation into injection drug use is essential for this effort and has been studied recently (11, 120, 122, 228). In one study, newly initiated injection drug users who were early attendees of shooting galleries (and thus engaged in a high risk social setting of injection) were 5 times more likely to share equipment (120). Longer-term injectors may serve as a potential access point for their younger, more newly initiated partners. Efforts to target these injectors and trainer these trainers in safer injection behaviors may be critical to reduction in risky behaviors and HIV and other blood borne infections among less experienced more newly initiated users.

Interventions to change behaviors are essential to limiting transmission, but they can consume a fair amount of resources. For interventions to be maximally effective, researchers must find out about successes or failures early so they can learn, change and improve. By using disease endpoint as the measure of efficacy, the research community is committed to knowledge turns of several years or more.

Andrew Grove, in a seminal article in *JAMA* in July 2005, suggested that the reason knowledge turns are so slow is due to the failure to take into consideration early endpoints (229). When we rely on surrogate endpoints, we are able to rapidly inform the hypothesis and generate results, which then lead to new hypotheses and new results. While his discussion focused primarily on the war on cancer, the message applies to all health disciplines and may be of value to research regarding prevention and intervention efforts for injection drug use.

In this analysis, the early endpoint is change in behavior. This change can be measured at 6 month intervals. The information generated can inform the project earlier and allow for additional interventions to be studied more rapidly. In addition, the intervention and the study can change and adapt as information is accumulated. Bayesian statistical methods are ideally suited for adapting to information that accrues during a study (230). Accumulating results can be assessed at any time – slowing or expanding accrual to a particular intervention, imbalancing randomization of interventions to favor better performing ones, and changing the study population of focus on subsets (such as drug users prior to initiation into injection or younger, more newly initiated IDUs) that are responding better to certain interventions. There is great potential of use of this methodology in behavioral studies to improve the effectiveness of interventions.

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APPENDICES

APPENDIX A: Dissertation Proposal
APPENDIX B: Revised Specific Aims (January 2013)

APPENDIX A: Dissertation Proposal

Injection practices and sexual behaviors by duration of injection among young, newly initiated injection drug users

A. SPECIFIC AIMS

The purpose of this study is to determine if levels of risky behavior among young, newly initiated injection drug users (IDUs) is higher in the first two years following initiation of injection drug use as compared to the next few years following initiation. A number of studies looking at prevalent and incident HIV infection have suggested that the risk of infection is higher immediately following initiation. Whether this higher risk of infection is due to higher levels of risky behaviors and/or lower levels of safer behaviors has not been established. This study will examine the prevalence of sexual behaviors and injection practices by duration of injection drug use, followed by a second analysis of the incidence of sexual behaviors and injection practices by duration of injection drug use. We hypothesize that newly, initiated IDUs are more likely to engage in riskier and less likely to engage in safer sexual behaviors and injection practices earlier in their injection career than during the later stages of their injection career.

The specific aims of the study are as follows:

1) to identify correlates and risk factors of HIV among young, newly initiated IDUs (duration of injection $\leq$ 2 years) and longer-term users (duration of injection > 2 years - 6 years), including demographic factors (age, sex, race, marital status, site of recruitment,

etc), sexual behaviors (trading sex for money or drugs, IDU-partner, condom use, etc), and injection practices (sharing needles and equipment, frequency and location of drug use, etc.)

2) to compare and contrast the above correlates of HIV seroprevalence between young, newly initiated IDUs and longer-terms users
3) to determine the incidence of "riskier" (converting from lower frequency of a behavior at baseline interview to higher frequency at the follow-up) and "safer" (converting from higher frequency of a behavior at baseline interview to lower frequency at the follow-up) sexual behaviors and injection practices among young, newly initiated IDUs and longer-term users.
4) to compare and contrast the incidence of riskier and safer sexual behaviors and injection practices between young, newly initiated IDUs and longer-term users

To address these aims, we plan to make use of questionnaire data from the Collaborative Injection Drug Users Study II (CIDUS II), a CDC-sponsored prospective study of young (18-29) and/or newly initiated IDUs (duration of injection < 3years). The study was conducted at six sites in five United States (US) urban areas: Baltimore, Chicago, Los Angeles, New Orleans, and New York City (Harlem and the Lower East Side). In this prospective study, investigators conducted risk interviews at baseline, and at two follow-up visits (6 month and 12 month) and obtained serum for HIV, HBV, HCV testing over a 2-year period.

B. SIGNIFICANCE

Overview

Injection drug use continues to be one of the major risk factors for acquisition of HIV, and, as of December 2001, accounted for over one-third of AIDS cases in the United States (1). Data from several studies of drug users in various regions in the Unites States have consistently reported a declining prevalence of HIV in the late 1990's among injectors (2-6). Des Jarlais and colleagues reported seroprevalences in New York City dropped from 44% to 22% from 1991 to 1996 among a street-recruited sample (3). However, newly Kottiri and colleagues showed a seroprevalence of 40% among a similar sample of IDUs (7). In addition, the CDC reported an increase in syphilis infections in 2001 -- the first spike since 1990 -- which raises concerns that the spread of STDs could lead to resurgence in HIV infections in this country (8). Studies in the former Soviet Republic, China, and India have also shown a recent rapid growth of HIV infection among drug users (9-12). Monitoring trends in the HIV epidemic, particularly in groups likely to engage in risk-taking behaviors, is crucial since HIV-seroprevalence patterns can change suddenly.

Several studies have reported higher HIV seroprevalence and seroincidence among young, newly initiated injectors than older, longer-term users (4, 6, 13). For example, Diaz and colleagues have shown that the risk of infection is higher soon after initiation of injection and stabilizes thereafter (14). Nicolosi and colleagues reported a higher rate of HIV seroconversion among IDUs within two years of initiation than among those who had been injecting longer than two

years (15). These studies report a 2-3 fold increased risk of infection among younger injectors. Understanding reasons for the variability in HIV incidence and prevalence rates among subgroups of IDUs is important for implementing appropriate prevention programs and controlling the transmission of HIV among IDUs.

In previous studies (see Preliminary studies: CIDUS and CIDUS –II), researchers have found that IDUs engaged in high levels of risky behaviors soon after initiation. Few studies to date have specifically examined injection practices among young, newly initiated IDUs. Doherty and colleagues reported that predictors of infection included still needing a person to inject them at least 60 days beyond initiation of injection and having at least 2 trainers (16). Fennema and colleagues demonstrated that younger IDUs were twice as likely to report current borrowing of equipment compared with older IDUs. Younger IDUs also reported lending used needles more and using needle exchange programs less (17). While these findings are important, further understanding of injection practices among young IDUs is needed.

Some studies have noted that young female IDUs have been found to be at greater risk of prevalent and incident HIV infection (18-20). This excess risk for women may be due to sexual behaviors other than injection practices – researchers attribute these higher rates to the additional impact of sexual transmission (20, 21). Since high–risk sexual behavior is usually initiated in adolescence or young adulthood, the question remains whether increased sexual risk-taking among adolescents explains the increased risk for this subgroup of IDUs. Further exploration of the relationship between sexual behaviors and duration of injection drug use is important.

Individual behaviors may not completely explain the increased risk of infection in this group. The group in which these users share equipment may also affect their chances of becoming infected. Previous studies have shown injecting with someone 5 or more years older is associated with increased risk of infection (22, 23). Further study of network characteristics for young injectors is needed to better explain the increased risk among this subgroup of IDUs.

Are risky behaviors elevated as soon as a person starts injecting? What are the characteristic behaviors? Is it sexual behaviors, injection practices and/or contact with older injectors? Do these behaviors become safer over time? The relative contribution of these factors to the HIV epidemic in this population is not well understood. Examining risk behaviors that are common early during the injection career may be key to explaining trends in HIV risk among IDUs. Understanding risky behaviors among recent initiates, the group likely at highest risk for HIV, is important for informing strategies for decreasing rates of HIV infection.

Public Health Impact of HIV

Over 20 years ago, on June 5, 1981, the Centers for Disease Control and Prevention reported 5 cases of Pneumocystis carinii pneumonia among gay men in Los Angeles (24). Two of the men were already dead. At the time, this seemed like a medical anomaly, and of interest to only a handful of health professionals. However, we now know today that this short article foretold the onset of the global epidemic of HIV/AIDS.

Today, the HIV/AIDS epidemic has killed an estimated 21.8 million people, and another 36.1 million are currently living with the HIV infection (25). Approximately 95% of these people are living in developing countries with minimal financial resources to deal with the epidemic, and where economic and social development is undermined by the heavy burden placed upon them by HIV/AIDS. Over 90% of those infected do not know that they have the disease (25). But even if they did, antiretroviral therapies (ART) are not an option for them at this time. The majority of those infected are of the age that they may be supporting children or the elderly or both.

In the United States, there are an estimated 850,000 to 950,000 people currently living with HIV, with approximately 40,000 new infections occurring in the US every year (26). Of new infections, 70% each year occur among men; however, women are also significantly affected. Men who have sex with men represent the largest proportion of new infections (42%), followed by heterosexual sex (33%) and injection drug use (25%)(26). Fifty-four percent of new HIV infections occur among blacks even though they only represent 12% of the US population. It is estimated that among new infections 26% are white and 19% are Hispanic, even though they make up only 13% of the US population (26). Since the beginning of the epidemic through June 2001, over 450,000 deaths due to AIDS have been reported (26).

HIV transmission among injection drug users

Injection drug use continues to be one of the major risk factors for acquisition of HIV, and, as of December 2001, directly and indirectly accounted for over 30% of AIDS cases in the United

States (1). HIV seroprevalence and seroincidence varies greatly among IDUs throughout the world (27). In certain regions, HIV seroprevalence among IDUs has remained fairly low, less than 5% and incidences has remained low in these settings as well, with rates of less than 1/100 person years at risk (1, 25, 26, 28). In other areas, seroprevalence has stabilized at much higher levels from 20-50% with incidences in the range of 4-8/100 person-years at risk (29-32). Finally, in certain populations, over 50% of IDUs are infected with HIV and incidences of 10/100 person-years at risk or higher have been reported (30, 33).

A. Developing world

The epidemic continues to spread in areas where the infrastructure for an effective response in not fully developed. In China, HIV prevalence has been reported as high as 82% among IDUs during 1998-1999 (9, 10). In India, the estimated infection rate among persons age 15-49 is 7/100 person-years at risk (9). In Thailand in the late 1980s, researchers saw a shift from a prevalence of 2% to one of almost 50% within one year (11). In response, health officials developed a surveillance systems and a response including a campaign of 100% condom use among sex workers. The public health program to prevent sexual transmission continues to be important; however, injection drug use has now emerged as an important risk behavior and is maintaining endemic HIV transmission in Thailand (9, 34). Eastern Europe has also had a recent rapid growth of HIV infection among drug users. In the Russian Federation, a prevalence of 56% among IDUs has been reported (9, 12). These new HIV epidemics in IDUs occurring in the former Soviet Republics, China and India suggest that this will be an important focus for intervention. Research to push forward knowledge on how to identify and stop epidemics early in IDU populations is urgently needed.

B. United States

In the United States, HIV seroprevalence among IDUs varies widely by geographic location. HIV seroprevalence has been found to be highest in the Northeast. Seroprevalences have been reported as high as 25% in Baltimore, 38% in Newark, and 53% in New York (3, 31, 35, 36). Low to medium seroprevalences have been reported in the Pacific and Mid-Atlantic States. Denver, Detroit, Los Angeles, San Francisco, San Jose, and Seattle have all reported seroprevalences ranging from 2 to 5% (31, 36-38).

Data from several studies among various populations in the United States have demonstrated declining seroprevalences in the late 1990s (4-6). Des Jarlais and colleagues reported a reduction in seroprevalence among IDUs in New York City from 1991 to 1996 with seroprevalences dropping among a street-recruited sample from 44% to 22% (3). However, recently Kottiri and colleagues reported a seroprevalence among a street-recruited sample of over 40% (7). In addition, the CDC reported an increase in syphilis infections in 2001 (8). This raises concerns that this could lead to resurgence in HIV infections.

Declining seroprevalence by itself cannot be seen as evidence of a declining epidemic. Prevalence may be declining due to loss of seropositive subjects due to death and migration out of the area of investigation, as well as other factors. Low seroprevalence must be coupled with low seroincidence to consider the epidemic to be in a declining phase. In the United States, seroincidence rates are consistent with seroprevalences. In the Pacific and mid-Atlantic regions, which reported low to medium prevalences, low seroincidence rates of 1/100 person-year at risk

or less were documented (31, 36). The areas of the US that reported higher prevalences (e.g., Baltimore and Newark), also reported higher incidences, with rates ranging from 3 to 5/100 person-years at risk (31, 39). Interestingly, although New York City reports one of the highest seroprevalences in the US, two studies have recently documented declining seroincidences in New York with rates ranging from 1/100 person-years at risk or less (36, 40). This may be evidence of a declining epidemic in New York possibly due to the impact of prevention efforts within this area. However, these results may be due to an oversampling of low risk IDUs -- older, more experienced users who practice safer practices. This proposed study provides the opportunity to research the injection practices of older versus younger injectors, which may help investigators to further explore the variations in incidence and prevalence trends among different populations of IDUs.

Correlates and risk factors of HIV infection among injection drug users

A. Correlates of HIV infection among IDUs

Numerous studies have examined the correlations between demographic factors, sexual behaviors and injection practices and HIV prevalence among IDUs. Demographic factors strongly correlated with HIV include race/ethnicity, socioeconomic status, and institutionalization (i.e., spent time in a correctional facility, jail, juvenile detention center, prison, mental health ward of a hospital or mental health facility) (6, 7, 41, 42). Correlations between race and prevalence of HIV infection probably are due to some unknown or unmeasured risk factor rather than to race itself. Socioeconomic status, much like race/ethnicity, is likely a proxy for some unmeasured factor associated with HIV infection.

Early in the HIV epidemic, heterosexual transmission did not appear to be an important method of acquiring the infection among IDUs (43). Researchers believed that injection practices were the primary source of HIV transmission and heterosexual transmission accounted for a negligible proportion of infections (44). Recent studies have shown that IDUs have substantial sexual risks for transmission of HIV and other blood borne infections (45),(39). Sex for money or drugs has also been correlated to HIV infection (16, 36, 46). Men having sex with men and having multiple sex partners have been shown to be associated with HIV seroprevalence as well (6, 16, 36).

Certain injection practices, which increase opportunities for exposure, have been associated with HIV infection. Sharing needles, attending shooting galleries, having multiple trainers before being able to self-inject are practices strongly correlated with HIV prevalence (16, 36). Evidence indicates indirect sharing such as backloading, frontloading and sharing of cookers (used to heat the drug), cotton (used to filter the drug), and water (used to rinse the needle) may also be associated with HIV transmission since this equipment, much like syringes and needles, may act as a reservoir of the HIV virus (47).

Injecting cocaine and smoking crack are both associated with HIV transmission (36). Since cocaine's effects are short-lived, addicts may require multiple 'hits' each day, which may result in a very expensive drug use habit. Research has shown that this can lead to the need to exchange sex for money and drugs (36). Cocaine does not have treatment substitutes –like methadone for opiates—so such findings may have a serious impact on drug treatment for cocaine users.

Finally, HIV prevalence tends to differ by age of the participant and duration of injection (defined as time since first injected). Some early studies suggested a direct and proportionate increase in prevalence of HIV infection with duration of injection (13, 48). These data seemed to show that seroprevalence of HIV is strongly associated with cumulative exposure. However, more recent studies have shown higher seroprevalence among more recent initiates (35, 38). These findings are supported by incidence data, which have shown that the risk of infection is higher soon after initiation of injection, and stabilizes thereafter (6, 14, 15). These data suggest that while patterns of dependence may be progressive, there are injection practices that may be present early in an injection career that confer risk for both acute and chronic infection. Although this hypothesis has yet to be adequately studied, this proposed study has the potential of better understanding the relationship between injection practices and duration of injection

B. Risk factors of HIV seroconversion

There are several advantages of studying incident cases as opposed to prevalent cases. First, risk practices that precede the infection can be disentangled from those that follow it. Second, incident studies can distinguish between factors that are related to the occurrence of the infection as opposed to those that are related to the severity and duration of the disease (correlates of prevalence). Finally, incident studies allow for the study of the natural history and progression of the disease as compared to prevalent studies, which cannot provide researchers with information regarding the natural history of the disease prior to the time of enrollment in the study (49).

Despite these advantages, incident studies of HIV infection among IDUs are difficult and expensive to conduct. Recruiting and retaining a sufficiently large enough sample of participants may be difficult, and if the participants who are lost to follow-up differ from those who remain in the study in terms of risk behaviors and infection rates, the result will be a biased estimates of the magnitude of the associations between risk behaviors and infection rates. Thus, there have been far fewer incident cohort studies of HIV infection among IDUs than prevalent cross-sectional studies of this same population.

Gender has been identified as a risk factor for HIV seroconversion (4, 18, 21, 39). Monterroso and colleagues reported a three-fold increase in seroincidence among women as compared to men (36). Solomon and colleagues attributed these higher rates to the additional impact of sexual transmission (21). Age has also been shown to be a key risk factor among IDUs (6, 50). Nelson and colleagues reported a seroincidence rate among young IDUs that was two times greater than older IDUs (4). More recently, Nelson and colleagues reported an even greater disparity in the incidence rates for younger versus older users -- incidence rates among younger injectors (< 30 years) were almost 3 times greater (rate ratio = 2.72, 95% CI, 1.89-3.92) than older injectors (> 40 years) (51).

Sexual practices that have been identified as risk factors for seroconversion include having multiple sex partners, having an HIV-positive sex partner, male homosexual behavior, and having an STD (21, 51, 52). Although seroprevalence studies have reported a correlation between trading sex for money or drugs and HIV seroprevalence, none of these studies reported this as a risk of seroconversion. However, smoking crack cocaine, which has been strongly

associated with trading sex for drugs or money, has been shown to be associated, with more than a two-fold increase in seroincidence (36).

Being a current injector and sharing and borrowing needles have been shown to be strong predictors of HIV seroconversion (4, 53, 54). Nelson and colleagues reported an association between HIV incidence and injection of cocaine, frequent injections, and injecting in a shooting gallery. Monterroso also reported frequent use of cocaine (greater than 5 times/day) as a risk factor (36).

Recent studies have also shown that the risk of HIV infection among IDUs is high during the early stages of the injection career, and that recent onset of injection is a predictor of seroconversion (17, 18, 32, 55, 56). Nicolosi and colleagues showed a higher rate of HIV seroconversion among IDUs within two years of initiation than among those who had been injecting longer than two years (15). Given the fact that across different studies the median age of initiating injection drug use is 20, age and duration of injecting are probably strongly correlated. Why is HIV incidence high early after initiation of injection drug use and why do rates decline after the first couple of years after initiation? In this proposed study, we hope to examine the relationship between duration of injection and injection practices in order to better understand these findings of increased rates among young and newly initiated IDUs.

HIV transmission among adolescents and young adults.

The incidence of HIV in the United States during the 1990s has fallen to levels below the peaks of the mid-1980s, but much of the decline reflects trends in white homosexual men older than 30 years (57). It is estimated that one in every four newly infected persons is younger than 22 and half of all new infections are among persons less than the age of 25. Because high–risk sexual behavior is usually initiated in adolescence or young adulthood, the epidemic continues to be propagated in this group (58). Adolescent and young adult populations are at particularly high risk of HIV infection from both unprotected sex and injection drug use. In fact, surveillance data indicates that rates of HIV infection were climbing for adolescent and young adult populations during the early 1990s (59). Increases were evident among minority females, young men who have sex with men, and homeless, abused, and runaway youths (59, 60). In 1998, Rosenberg and Biggar reported two major trends in HIV incidence among adolescents and young adults. Incidence among young homosexual men and IDUs was beginning to slow, but heterosexual transmission, especially among minorities, was increasing (5). However, recent HIV surveillance data show increases in the number of cases reported among minority young (age 13-29) adults who inject drugs and among young men who have sex with men (2). In fact, studies of sexually transmitted diseases (STDs) and sexual behaviors suggest a resurgent HIV epidemic among men who have sex with men (61, 62).

HIV transmission among young, newly initiated injection drug users

A. HIV prevalence and incidence studies among young, newly initiated IDUs

Young, newly initiated IDUs are often difficult to locate and recruit for studies because of their hesitancy to self-identify and their limited connection to health care and drug treatment services.

Therefore, to date, there have been few studies conducted using this population. HIV seroprevalence among young, newly initiated IDUs is often lower than for older, longer-term users. For example, in Amsterdam, researchers report prevalences for young, newly initiated IDUs ranging from 12-24% (as compared to 34% among older, longer-term users)(17, 53). In the northeast US, prevalences among young, newly initiated IDUs tend to be the highest, with values ranging from 10-20% (6, 23, 50). Recently, in a small sample (n = 276) of young IDUs, Fuller and colleagues observed a seroprevalence rate of 11% (63).

Seroincidence information on this population is minimal as well. Several studies have reported higher incidence among young, newly initiated injectors than older, longer-term users (4, 6, 13). High incidence rates may be particularly common among new injectors in regions of moderate to high seroprevalence (50). Fennema and colleagues reported an incidence rate of 18/100 person years at risk for younger injectors as compared to 9.5/100 person years at risk for longer-term users during the same time period (17, 32). In a study conducted in Baltimore, Fuller and colleagues recently reported one of the highest HIV incidence rates observed (annual incidence of 6.6 per 100 person-years) among young, newly initiated IDUs (63). Better understanding of risk behaviors among younger IDUs may help to explain trends in seroprevalence and seroincidence for this group.

B. Definition of a newly initiated IDUs

There is no firm definition of the newly initiated injector. Researchers define the newly initiated injector by duration of injection drug use, using various time frames-- less than 2 years, less than five years, and less than 10 years. These definitions are more of a statistical construct than a

theoretical one. Originally, researchers theorized that the prevalence of HIV among new injectors would be lower than longer-term users because of the shorter duration of potential exposure. Researchers thought that new injectors were less likely to share equipment and if they did so, they were more likely to share with other newer injectors, who were less likely to be infected. Plus, if people started injecting despite the knowledge that HIV can be spread through the use of shared equipment, it was hoped that they would follow safer injection practices (13). Unfortunately, this was not the case. In a study of drug injectors recruited from locations where drugs were being sold openly, researchers found that more experienced users were taking more precautions than new injectors. As duration of injection increased so did the percentage of injectors who engaged in less risky behavior -- 16% of injectors of less than 2 years changed their behaviors to reduce risk, compared to 29% of injectors of 3-5 years, 33% of injectors of 6-10 years and 66% of injectors of greater than 10 years (64).

The behavior patterns of individuals may not fully explain the prevalence of HIV infection among new IDUs. The group in which these users share equipment may also affect their chances of becoming infected. Thus, it has become important to study the social dynamics of groups of people who are new injectors. Typically, a friend of relative initiates a new injector (13, 65, 66). Since the injection may not be planned and the new injector may not be committed to continued injection, the new injector almost never has his/her own equipment and must borrow from the friend or relative. There is limited information characterizing the friends or relatives who initiate the new injector, but one theory is that these initiators are relatively new to injection drug use and are not experiencing problems related to their drug use (13, 65). Groups of uninfected friends and acquaintances continue to inject with one another over a period of some months and

then some begin to interact with a broader injection network than may consist of older injectors (13). Some researchers believe that this lack of contact with older injectors in the first several months may be the reason why newer injectors do not practice safer techniques. Investigators hypothesize that as new injectors gain greater contact with more experienced users they increase their awareness of AIDS and safer injection techniques, but they also increase their probability of sharing equipment with someone infected with HIV (13). An early study confirmed this hypothesis by showing a direct and proportionate increase in risk for injection with duration of injection (6).

However, additional studies of HIV seroprevalence and seroincidence found newer injectors are at the greatest risk of HIV soon after initiation of injection (4, 6, 14, 15). Results from these studies showed younger IDUs have a 2 to 3-fold risk of HIV infection as compared with older IDUs. Garfein and colleagues showed one predictor of a blood borne infection among IDUs included injecting with someone 5 or more years older (OR = 2.99, 95% CI, 1.43-6.23) (22). Diaz and colleagues also report in a study of Latinos in New York City having been given the injection by someone who was 5 or more years was associated with HIV infection (23). Contact with these older users early in the injection career might be the reason for the infection rates in younger injectors. Further study of network characteristics for young injectors is needed to better explain the increased risk among this subgroup of IDUs.

Correlates of seroprevalence and risk factors for seroconversion among young, newly initiated injection drug users

Although recent studies have noted higher risks of HIV infection among young, newly initiated IDUs, data on risk factors for these younger IDUs are limited. In terms of demographic factors, several studies have found that young female IDUs are at greater risk of prevalent and incident HIV infection (18-20, 36). This excess risk for women may be due to sexual behaviors other than injection practices – Miller and colleagues report that HIV seropositivity is concentrated among females engaging in both sexual and drug-related risk categories (20).

Data on sexual behaviors for young, newly initiated IDUs indicate that risks are similar for young, newly initiated IDUs as compared to longer-term users. Sexual behaviors shown to have stronger association with HIV among young IDUs include: male homosexual behavior, trading sex for money or drugs, and having multiple partners (6, 16, 17).

Few studies to date have specifically examined injection practices among young, newly initiated IDUs. Zinberg noted with qualitative studies that IDUs tended to be initiated by persons who recently began injecting, indicating a pattern of entry where injection practices are performed by others until the IDU develops the competency to self-inject (65). Doherty and colleagues showed that predictors of infection among new IDUs included still needing a person to inject them at least 60 days beyond initiation of injection and having at least 2 trainers (16). Fuller and colleagues showed that HIV prevalence was significantly associated with early shooting gallery attendance (OR = 3.1, 95% CI = 1.2-8.4), and early shooting gallery attendees were more than two times more likely to be initiated by someone at least 5 years older (63). These findings seem to suggest that higher risk among young IDUs may be the result of specific practices related to and influenced by initiation into injection drug use. Fennema and colleagues, in a study

comparing trends in risk behaviors and HIV incidence among subgroups of IDUs, demonstrated that younger IDUs were twice as likely to report current borrowing of equipment compared with older IDUs. Younger IDUs also reported lending used needles more and using needle exchange programs less (17).

While these studies are important, confirmation of these findings is crucial. This proposed study would allow us to investigate whether risky behaviors are higher soon after onset of injection among a larger population in multiple cities. This proposed study would allow us the opportunity to better understand one subgroup of injectors. Is it important to target specific behaviors? Which behaviors? By conducting this proposed study, we will attempt to determine if IDUs are more likely to engage in certain injection practices and sexual behaviors earlier in their injection career than they would as longer-term users, supporting the findings of increased rates of bloodborne infections in this group of injectors

Using data from a multisite prospective cohort study, we will conduct a two-part analysis of the association of risk–taking behaviors and duration of injection drug use. First, we will conduct an analysis of data collected at the baseline interview to determine whether certain recent risk behaviors were more common among IDUs in the first two years after initiation as compared to those who have injected for more than two years. We will follow this up by examining incidence of riskier and safer behaviors from the baseline to the 6-month follow-up interview by duration of injection drug use. By conducting these analyses we can examine behaviors at baseline as well as behavioral changes over time to determine why HIV seroconversion rates are highest early in the injection career and then subsides. Is it because behaviors become safer over time?

Future implications

IDUs may not openly identify themselves as such, and they may be less likely to seek out health care and drug treatment programs. Young or newly initiated IDUs in particular may be especially unwilling to utilize such services. For this reason, newly initiated IDUs may be more difficult to identify for prevention efforts. Particular attention should be paid to locating these subjects, and providing them with appropriate prevention programs.

If we can determine behaviors in the early phase that are predictive of increased risk of infection, we would know that it is important to target specific behaviors for this subgroup of IDUs. We may find that sexual transmission is an important mode of transmission among younger IDUs. In this event, prevention efforts could include a strong emphasis on safer sexual practices. If our data support the idea that engaging in certain risky injection practices are the reason for the increased risk in this group, younger IDUs should be educated to practice safer injection techniques. Should the increased risk be due to contact with older IDUs who act as reservoirs of the infection, prevention efforts could be directed to older IDUs who are likely to have early contact with this population.

Understanding trends among new initiates into injection drug use may be important for determining strategies for controlling the epidemic in this population. Reaching this population at risk to ensure early diagnosis as well as sustained access to preventive and treatment services can have a major impact on the HIV and AIDS epidemic.

C. PRELIMINARY STUDIES

1. The Collaborative Injection Drug Users Study (CIDUS)

CIDUS was conducted to look at the natural history of HIV infection among IDUs. This study was conducted in 5 US cities, Baltimore, Chicago, Los Angeles, New York (Harlem and the Lower East Side), and San Jose(36). Participants were recruited through word-of-mouth at a variety of community agencies including drug abuse treatment clinics, city health department clinics for STDs, local emergency rooms, state probation and parole offices, university hospitals, HIV-AIDS clinic, and street outreach AIDS prevention programs of a local community education group. Eligibility requirements included being 18 years of age or older and having a history of injection drug use at any time since 1977. Over 3000 IDUs were recruited, and the study has identified almost 650 prevalent cases and over 300 seroconverters. The results of this study showed higher incidence in younger IDUs as compared to older IDUs (67) These data suggest that there may be behaviors early in the injection career that increase the risk of infection during this period. In this proposed study, we would examine injection practices and sexual behaviors of IDUs soon after the initiation.

2. The Collaborative Injection Drug Users Study II (CIDUS–II)

In response to the surprising findings of CIDUS that younger injectors were at increased risk of infection, CIDUS-II was conducted to identify the prevalence and correlates of HIV infection

among young (18-30) and newly initiated (duration <3 years) IDUs. For this study, one site was dropped from the CIDUS project, San Jose, while another was added, New Orleans. Participants were recruited through street outreach, treatment programs, local emergency rooms, and health clinics. Participants underwent a baseline interview, venipuncture, and HIV-testing with pre-and post-test counseling, and up to 2 follow-up interviews (6 and 12 months later) and HIV testing (for seronegative participants).

Factors associated with HIV included having numerous partners, identifying as gay or bisexual, having been sexually assaulted, trading sex for drugs or money following initiation, and having greater than 2 trainers before being able to self-inject (6, 16). The results of this study seem to confirm that higher levels of risky behavior are present soon after onset of initiation. Further evaluation of the risk-taking behaviors of these young injectors is needed to explain the patterns of seroconversion seen in this study. Further research is needed to determine if certain risky behaviors are elevated early in the injection career and subside as the injection career progresses. This proposed study will attempt to determine if behaviors become safer over time.

D. STUDY DESIGN AND METHODS

The specific aims of this dissertation will be addressed by performing two separate analyses, baseline and follow-up analyses, using a multisite prospective cohort study. For Aims 1 and 2, recent and 6-month histories of personal characteristics (sexual behaviors and injection practices) reported at baseline will be identified and assessed for association with duration of injection drug use. To address Aims 3 and 4, changes in the frequency of recent and 6-month histories of

sexual behaviors and injection practices from baseline to 6-month follow-up interview will be calculated and associations between the changes in the frequency of these behaviors and duration of injection drug use will be estimated. This proposed study will attempt to identify new and validate previously reported sex and drug risk correlates and risk factors for HIV infection among young, newly initiated IDUs. Both analyses will make use of questionnaire data from the Collaborative Injection Drug Users Study - II (Principle Investigators, alphabetically: Don Des Jarlais, Richard Garfein, Peter Kerndt, Edward V. Morse, Lawrence Ouellet, Steffanie A. Strathdee, and David Vlahov) hereafter referred to as CIDUS-II.

1. Background and hypothesis

The main objective of this analysis will be to determine if young, newly initiated IDUs are more likely to engage in certain injection practices and sexual behaviors earlier in their injection career than they would as longer-term users.

A. Baseline analysis

In the first analysis, we will use the baseline interview data to ascertain if the prevalence of certain injection practices and sexual behaviors differed by duration of injection. Specific questions to be addressed in this analysis are the following:

1. Recent injection practices and sexual behaviors

Are IDUs of 0-1 years and 2-3 years more likely to engage in certain recent riskier injection practices (i.e., inject with others the last time they injected and inject more now

than in the last 6 months) and sexual behaviors (i.e., not using a condom last time had sex) than IDUs of 4-6 years? The study hypothesizes that IDUs of 0-1year and 2-3 years are more likely to engage in these recent riskier injection practices and sexual behaviors than IDUs of 4-6 years.

2. Riskier injection practices and sexual behaviors in past 6 months

Are IDUs of 0-1 year and 2-3 years more likely to have engaged in riskier injection practices (i.e., needle sharing, backloading, sharing of cookers, cotton, and rinse water) and sexual behaviors (i.e., having partners who are IDUs and giving and receiving drugs or money for sex) during the past 6 months than IDUs of 4-6 years? The study hypothesizes that IDUs of 0-1 year and 2-3 years are more likely to engage in these riskier injection practices and sexual behaviors than IDUs of 4-6 years.

3. Safer injection practices and sexual behaviors in the past 6 months

Are IDUs of 0-1 year and 2-3 years less likely to engage in certain safer injection practices (i.e., used new needles, getting new needles from NEP, using bleach on used needles) and sexual behaviors (i.e., using a condom with steady and casual partners) than IDUs of 4-6 years? The study hypothesizes that IDUs of 0-1 year and 2-3 years are less likely to engage in certain safer injection practices and sexual behaviors in the past 6 months than IDUs of 4-6 years.

B. Follow-up survey analysis

In the second analysis, we will use the baseline and follow-up interview data to examine changes in injection practices and sexual behaviors among study participants over time. We will determine if incidences of riskier and safer injection practices and sexual behaviors from the baseline to the follow-up interview varied by duration of injection. Specific questions to be addressed in this analysis are the following:

1. Incidence of recent injection practices and sexual behaviors

   Are the incidences of riskier recent injection practices (i.e., injecting with others the last time you injected and inject more now than the last time you injected) and sexual behaviors (i.e., did not use a condom the last time you had sex) greater for IDUs of 0-1 year and 2-3 years than IDUs of 4-6 years? The study hypothesizes that the incidences of riskier recent injection practices and sexual behaviors will be greater for IDUS of 0-1 year and 2-3 years than IDUs of 4-6 years.

2. Incidence of riskier injection practices and sexual behaviors in the past 6 months

   Are the incidences of riskier injection practices (i.e., needle sharing, backloading, sharing of cookers, cotton, and rinse water) and sexual behaviors (i.e., having partners who are IDUs, and giving and receiving drugs or money for sex) in the past 6 months greater for IDUs of 0-1 year and 2-3 years than IDUs of 4-6 years? The study hypothesizes that the incidences of riskier injection practices and sexual behaviors in the past 6 months will be greater for IDUS of 0-1 year and 2-3 years than IDUs of 4-6 years.

3. Incidence of safer injection practices and sexual behaviors in the past 6 months

Are the incidences of safer injection practices (i.e., using new needles, getting new needles from NEP, using bleach on used needles) and sexual behaviors (i.e., using a condom with steady and casual partners) in the past 6 months lesser for IDUs of 0-1 year and 2-3 years than IDUs of 4-6 years? In other words, are the incidences of safer injection practices and sexual behaviors greater for IDUs of 4-6 years than IDUs of 0-1year and 2-3 years? The study hypothesizes that the incidences of safer injection practices and sexual behaviors in the past 6 months will be greater for IDUs of 4-6 years than IDUs of 0-1 year and 2-3 years.

2. Study Design: Cross-section and cohort study

The study population for this cross-sectional survey with a longitudinal cohort follow-up component was recruited between 1997-1999 as part of CIDUS-II, a multisite prospective cohort study funded by the Centers for Disease Control and Prevention (CDC). The study was conducted at six sites in five US urban areas: Baltimore, Chicago, Los Angeles, New Orleans, and New York City (Harlem and the Lower East Side). A uniform protocol was developed across all sites for recruitment, eligibility, baseline and 6-month follow-up assessment. Informed consent was obtained from all participants prior to study enrollment, interview, and venipuncture. The study received approval from the CDC and the institutional review boards at each of the participating sites.

A. Population

A cohort of 2435 IDUs was recruited and completed the initial interview and HIV, HBV, and HCV testing. Due to the difficulty in recruiting young (15-29 years) and newly initiated IDUs (duration of injection < 6 years) many of the sites relaxed the eligibility criteria (See 4. Eligibility criteria) and recruited participants who were older (>30 years) and injecting drugs for more than 6 years. Individuals were asked to return for a second interview and serum test 6 months later to ascertain any changes in injection practices and sexual behaviors. For the baseline analysis (Aims 1 and 2), 599 will be excluded because of missing information on duration of injection (2) or injecting for more than 6 years (597). Of these 1836 participants, 1244 (68%) completed the follow-up interview and will be included in the follow-up analysis (Aims 3 and 4). The demographic features of those enrolled in CIDUS-II are as follows: median age = 23 years, median duration of injection = 3 years, 63% are men, 39% are African-American or Latino, 49% reported being homeless in the last 6 months, and 43% reported being institutionalized in the last 6 months.

B. Eligibility Criteria

Criteria include having begun to inject illicit psychoactive drugs for the first time within 6 years of enrollment and having injected at least once in the past 6 months. Injection status was verified by the presence of injection stigmata, (scar tissue or tracks) and via a series of questions designed to assess the plausibility of an individual's experience injecting drugs. Initially, participant ages ranged from 15-29 years and were verified by presentation of a current piece of identification with photo and birth date. However, the upper limit of the age range was removed

due to difficulty in recruitment of this population. All participants had to agree to HIV testing, counseling, and learning of the test results.

3. Recruitment and Retention

Community-based convenience sampling methods were used to recruit participants. Certain sites (e.g. NDRI, NYAM and Baltimore) used ethnographic mapping to identify areas where drug using and selling were particularly prevalent, whereas other sites (e.g. Chicago and Los Angeles) did not use not use formal mapping but rather used previous knowledge of areas where IDUs were known to congregate. Trained recruiters conducted outreach efforts in these identified areas by approaching young, likely looking people, engaging them in causal conversation, and assessing the eligibility by asking a series of structured questions. Those found to be eligible were escorted to the study office to receive baseline screening and to provide informed consent or, at NDRI, told to call the office for telephone screening prior to being accompanied to the office (if found to be eligible). All participants were given a small payment ($25) for their time after they completed the interview.

Since young and newly initiated IDUs are often difficult to locate, additional methods were used for recruitment including: utilizing informal chain referral; advertising in alternative newspapers (Chicago); posting flyers at college campuses (Chicago), emergency rooms (Baltimore), health clinics (Baltimore), youth shelters (Baltimore), and NEPs (Chicago, Baltimore, NYAM); and distributing information in areas with high prevalence of young drug users (NDRI). Baltimore, Los Angeles and NYAM used mobile clinics to increase their accessibility. Chicago also

contacted participants through respondent-driven sampling (i.e., participants were given 3-6 coupons for distribution to other young IDUs; when a qualified participant returned the coupon to attempt to enroll in the study, the recruiter who provided the coupon was reimbursed $10).

To assure retention in the cohort, several methods were employed to facilitate a high return rate to the follow-up interview including mailed reminders, travel vouchers for public transportation to visits, tracing through contacts, and a modest honorarium for time and effort. At the baseline assessment, each participant filled out a locator sheet with contact information, usual hangouts and location of recruitment, and contact information was verified immediately following interview. Participants were sent reminders to return for the test results 2 weeks after the baseline assessment.

Prior to the follow-up interview, participants receive a reminder letter (2 weeks prior) and reminder telephone calls (both 1 week and 1 day prior), if possible. If the participant missed the visit, a letter was sent and, if necessary, participants were traced using the information provided on the locator sheet.

4. Data collection

A. Field procedures

Eligible and consenting participants underwent standardized face-to-face interviews as well as venipuncture at baseline and follow up. Pre-test counseling was given on the serologic tests (HIV, HBV, and HCV infection) to be conducted and on ways to reduce risky behaviors

associated with the transmission of each infection. To minimize potential bias, interviews were conducted prior to pre-test counseling and venipuncture. All participants were given appointments to return to receive their test results and were given post-test counseling.

B. Interview

The baseline interview obtained information on sociodemographics, alcohol and drug use, injection practices, sexual behaviors, and institutionalization (i.e., spent time in a correctional facility, jail, juvenile detention center, prison, mental health ward of a hospital or mental health facility). Sociodemographic questions included site of recruitment, marital status, and history of homelessness. Injection practice questions focused on the recent history of frequency, duration, and location of drug use, and the sharing of equipment including cotton, cookers, and rinse water. Sexual behavior questions included condom use, giving and receiving drugs or money for sex, and whether partners used injection drugs.

The 6-month visit included all the above baseline information with the exception of the fixed demographic characteristics, and the question asking if injected with others the last time injected (question C24 from the baseline interview: “The last time you shot, did you shoot-up with other people? [Shooting up with others who were also shooting up at the same time]”).

5. Data preparation

All variables to be used in the data analyses will be checked for errors, inconsistencies, and outliers. All continuous variables for exposures and potential confounders will first be examined as categorical variables, and results using the categorized variables will be plotted on a log scale

to check for linearity. If variables are shown to be linear, they will be kept in the model as continuous. Whenever possible, continuous variables with missing data will be analyzed using both mean substitution and removal of the subjects with missing or incomplete data. If these results differ, analyses will be performed and presented both with and without mean substitution.

6. Data analytic strategy

A. Baseline study (Aims 1 and 2)

In order to focus on newly initiated IDUs, this analysis will be restricted to participants who report drug use for no more than 6 years using the limit established by Garfein (6). While the study sample consists of 2435 participants, 599 will be excluded because of missing information on duration of injection, more specifically age of first injection (2), or injecting for more than 6 years (597). Therefore, 1836 participants will be included in this analysis.

Study participants will be divided into three groups (serial cross-sections) based on duration of injection: 0 to 1 years, 2 to 3 years, and 4 to 6 years. Among the 1836 participants to be included in the analysis, 34 % had been injecting for 0 to 1 years, 38 % for 2 to 3 years, and 28 % for 4 to 6 years.

1. Derivation of variables

Descriptions of the derivation of variables central to the baseline analysis are provided below:

1a. Duration of injection

Duration of injecting will be derived from information collected from two questions in the CIDUS II baseline survey – age of first injection (Question C26A, "How old were you when [you first injected an illicit drug]?") and age at baseline interview (Question B1A, "How old does that make you?"). Duration of injection will be calculated from age of first injection to age at baseline interview.

1b Recent injection practices

Information based on the participants' last encounter with injection drugs appear to best represent the participants' most recent injection practices, and information on the participant's last sexual encounter seemed to best represent the participants most recent sexual behaviors. Therefore, the following two questions regarding injection practices and one question regarding sexual behaviors from the CIDUS-II baseline interview were identified as good proxies of the study participants' most recent behaviors:

> Question C24: The last time you shot, did you shoot-up with other people? [Shooting up with others who were also shooting up at the same time]

> Question E4: Do you now inject on average: more than you did in the last six months, less than you did in the last six months or about the same as you did in the last six months?

Question G15B: The last time you had sex, did you or the person you were with use a condom?

Hereafter, question C24, injecting with others the last time you injected, will be referred to as "inject with others," and question E4, injecting on average more than in the last 6 months will be referred to as 'inject more now." Question G15B, using a condom that last time you had sex, will be referred to as, "no condom last time." Of the 1836 participants included in the analysis, 7 were missing data on "injects with others, " 1 was missing data on "injects more now," and 191 were missing data on "no condom last time."

2. Frequencies for demographic characteristics, injection practices and sexual behaviors

Frequency distributions of select demographic characteristics, injection practices, and sexual behaviors stratified by the three groups (categorized by duration of injection) will be performed in order to look at the proportion of participants in each serial cross-section by these specified factors. Chi square tests for trends will also be performed to determine if there is a linear trend between duration of injection and the frequency of each of the injection practices and sexual behaviors studied.

3. Unadjusted analyses for injection practices and sexual behaviors by duration of injection

Unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated to examine the risk of engaging in select injection practices and sexual behaviors by

duration of injection. Participants who injected for 4 to 6 years will be used as the reference group given the study hypothesis that this group will engage in the least risky behavior. The primary analysis will involve examining the relationship between duration of injection and two recent injection practices, injecting with others the last time you injected ("inject with others") and injecting on average more than in the last 6 months ('inject more now") and one recent sexual behavior ("no condom last time"). Secondary analyses will include examining injection practices and sexual behaviors in the last 6 months to determine the relationship between these factors and duration of injection. There may be some degree of within cluster correlation resulting from the fact that participants from a given site of recruitment may tend to resemble each other more then they resemble subjects from the other sites. Failing to account for clustering should not affect the odds ratios but may result in confidence intervals that are falsely narrow. Therefore, a correction factor for the variance that makes adjustments for the presence of intracluster correlations will be utilized when calculating interval estimates of the odds ratio (68, 69).

4. Multivariate analyses for injection practices and sexual behaviors by duration of injection

Multivariate logistic regressions will be performed in order to determine adjusted associations between duration of injection and the primary outcomes of interest (inject with others, inject more now, and no condom last time). The analyses will adjust for demographic factors that differ appreciably for the three injection groups. Variables will be selected based on prior knowledge and credibility given the available information

regarding the relationship between certain sociodemographic factors and injection drug use (70). Since the outcomes of interest are risk behaviors, other risk behaviors will not be controlled for in the multivariate models because of the high correlation between these behaviors. Multivariate logistic regressions also will be performed to determine adjusted associations between duration of injection and injection practices and sexual behaviors in the last six months. As with the univariate analysis, a corrected variance will be utilized to calculate confidence limits for the adjusted odds ratios.

5. Assessment of Interaction

Interaction terms will be fitted to the models to investigate whether associations between the primary outcomes of interest (inject with others, inject more now, no condom last time) and duration of injection differ by site of recruitment. The interaction terms will represent the product of the site variable (each site versus all other sites) by duration of injection. We will also examine if associations between the primary outcomes and duration of injection differ by race/ethnicity. The interaction terms will be the product of the race/ethnicity variable (white versus all others, black versus all others and Hispanic versus all others).

Interaction will be assessed via formal tests of interaction on a multiplicative scale and through stratified analyses. The difference between –2log likelihood estimates of models with and without interaction terms will be compared to a chi-square distribution with degrees of freedom equal to the difference between the number of parameters in the two models. The interaction will be considered significant if the p-value is less than 0.05.

B. Follow-up study (Aims 3 and 4)

In order to make comparisons of results from baseline study to the follow-up study participants included in the first study will be included in the follow-up study if they completed the follow-up interview. Of the 1836 participants included in the baseline analysis, 1244 (68%) completed the follow-up interview and will be included in the follow-up analysis.

1. Derivation of variables

Descriptions of the derivation of variables central to the follow-up analysis are provided below:

1a. Duration of injection:

Participants will retain their injection category from the baseline analysis (See 6A. Baseline Study). Duration of injection will be calculated as age of first injection (Question C26A from baseline interview) to age at baseline interview (Question B1A from baseline interview).

1b. Recent injection practice and sexual behaviors:

Responses to questions regarding recent injection practices and sexual behaviors of interest were measured on a dichotomous scale: 0 = no, 1 = yes and a trichotomous scale: 1 = more, 2 = less, 3 = same. Changes in responses to the questions from the baseline to the follow-up interview will be categorized in one of three groups: decrease, no change, or increase. Examples of possible changes in recent injection practices and

sexual behaviors from the baseline to the follow-up study, which may emerge appear in Table 1, below:

Table 1. Examples of possible changes in injection practices and sexual behaviors from the baseline to the follow-up study

Variable of Interest (Recent behaviors)	Baseline Response	Follow-up Response	Interpretation
Inject with others or No condom last time (possible responses = no, yes)	Yes	Yes	No Change – continued riskier behavior
	Yes	No	Decrease in Riskier Behavior
	No	Yes	Increase in Riskier Behavior
	No	No	No Change – continued safer behavior
Inject more now (possible responses = more, less, same)	More	More	Increase in riskier behavior
	More	Less	Decrease in riskier behavior
	More	Same	No Change – continued riskier behavior
	Less	Same	No Change – continued safer behavior

1c. Injection practices and sexual behaviors during the last 6 months

Responses to questions regarding injection practices and sexual behaviors during the last 6 months were measured on a 7-point scale: 0 = Never, 1 = Once a month or less, 2 = Two to three days a month 3 = About once a week, 4 = Two to three days a week, 5 = Four to six days a week, 6 = Everyday. Certain questions that did not lend themselves to such detailed responses from participants regarding frequency were measured on a 5-point scale: 0= Never, 1 = Less than half the time, 2 = About half the time, 3 = More than half the time, 4 = Always.

Changes in behaviors, during the last 6 months from the baseline to the follow-up interview, will be calculated by subtracting the frequency at baseline from the frequency at follow-up for each of the behaviors.

Riskier injection practices and sexual behaviors at the follow-up interview as compared to the baseline interview will be defined as converting from a lower to higher frequency of a behavior from the baseline interview to the follow-up interview. Specifically, the difference in frequency of behavior from baseline to follow-up will range from –1 to -6.

Safer injection practices and sexual behaviors will be defined as converting from a higher to a lower frequency of a behavior from the baseline to the follow-up interview. In other words, the difference from baseline to follow-up will range from 1 to 6.

Unchanged behaviors from the baseline interview to the 6-month follow-up interview will be defined as the difference in frequency from the baseline to the follow-up equaling 0.

Examples of possible changes from the baseline to the follow-up interview in injection practices and sexual behavior in the last 6 months, which may emerge appear in Table 2, below:

Table 2. Examples of possible changes from the baseline to the follow-up interview in injection practices and sexual behaviors in the last 6 months

Examples of variables of interest (behaviors in the last six months)	Baseline response	Follow-up Response	Change in Risky Behavior	Interpretation
Needle sharing – follow someone	0	4	-4	Riskier practices at follow-up
	5	3	1	Safer practices
	6	6	0	No change
Backloading	2	3	-1	Riskier practices
	4	2	2	Safer practices
	3	3	0	No change

*Note: Value labels: 0 = Never, 1 = Once a month or less, 2 = Two to three days a month 3 = About once a week, 4 = Two to three days a week, 5 = Four to six days a week, 6 = Everyday

2. Frequency distributions of select demographic characteristics, injection practices and sexual behaviors

Frequency distributions of select demographic characteristics, injection practices, and sexual behaviors stratified by the three groups of IDUs (0-1 year, 2-3 years, and 4-6 years) will be performed in order to look at the proportion of subjects in each group by these specified factors at the follow-up interview. Comparisons will be made with the frequency distributions from the baseline analysis. In addition, we will conduct Chi square tests for trend to determine if there is a linear trend between duration of injection and the frequency of each of the injection practices and sexual behaviors examined.

3. Univariate analysis

Incidence of riskier behaviors will be calculated by dividing the number of events by the number of study participants at risk stratified by duration of injection. An event will be defined as engaging in a behavior less frequently at baseline than at the follow-up interview.

Odds ratios and 95% CIs will be calculated using logistic regression. Subjects who injected for 4 to 6 years will be used as the reference group given the study hypothesis that this group will engage in the least risky behavior. Since within cluster variances may be smaller than would be expected if participants were randomly assigned to site of

recruitment, adjustment factors for the variances will be applied when calculating the confidence limits.

One current drug risk behaviors (question E4 on the baseline and follow-up interviews, "Do you now inject on average: more than you did in the last six months, less than you did in the last six months or about the same as you did in the last six months?), 'inject more now", and one current sex risk behavior (question G15 on the baseline and question G16 on the follow-up study, "The last time you have sex did you or the person you were with use a condom?") "no condom last time", are the primary outcomes of interest since they are considered good proxies of the study subjects' most recent behaviors. The follow-up interview did not include question C24 from the baseline interview, "The last time you shot, did you shoot-up with other people? [Shooting up with others who were also shooting up at the same time]," so changes in this behavior from the baseline interview to the follow-up interview cannot be explored.

Secondary analyses will include examining incidence of riskier injection practices and sexual behaviors in the last 6 months by duration of drug use.

4. Multivariate analysis

Multivariate logistic regressions will be performed in order to determine adjusted associations between years of injecting drug use and riskier current behaviors (inject more now and no condom last time) as well as injection practices and sexual behaviors in the last 6 months. As with the baseline analysis, this analysis will adjust for demographic

factors that differ appreciably for the three injecting drug use groups. Variables will be selected based on prior knowledge and credibility given the available information regarding the relationship between certain sociodemographic factors and injecting drug use (70). Since the outcomes of interest are risk behaviors, other risk behaviors will not be controlled for in the multivariate models due to the high correlation between these behaviors.

Although study subjects were expected to return at 6 months for follow-up interviews, time to follow-up interviews ranged from 3 months to 26 months (median time to follow-up interview = 6.7 months). Since those with longer time to follow-up have an increased chance of having an event (inject with others, inject more often, etc.), this analysis will also adjust for length of time from baseline to follow-up interview. Corrected variances, accounting for correlations between responses from IDUs at the same site of recruitment, will be used to calculate confidence limits for the adjusted odds ratios.

5. Additional analyses

5a. Incidence of safer injection practices

The analysis will also include calculating incidence (# events/ number of study subjects at risk) of safer injection practices by duration of injection drug use. An event will be defined as engaging in the behavior more frequently at baseline than at the follow-up interview. Logistic regressions will be performed to determine the odds ratios of safer injection practices and sexual behaviors by duration of injecting drug use

5b. Incidence of unchanged injection practices

Analysis will also include characterizing the subjects whose behaviors did not change from the baseline interview to the follow-up interview (if the sample size permits).

6. Loss-to-follow up from baseline interview to follow-up interview

Among the 1836 participants are included in the first analysis, 1244 participants completed the follow-up interview (68%). Thus, the analysis will also include evaluating potential biases from loss to follow up to guard against errors in internal validity.

We will compare those who returned for the follow-up interview and those who did not in terms of demographic factors and behavioral ones. We will also compare the proportion of the shorter-term (0-1 year and 2-3 years) and the longer-term injectors (4-6 years) in terms of these variables to determine if there is greater variability among the participants who completed the follow-up versus those who did not by duration of injection. Finally, we will re-analyze the baseline data restricting the analysis to those participants who did not complete the follow-up interview to determine how these participants look on the baseline values for the 3 groups.

Previous studies have found that risk factors for those who drop out and those who returned may offset each other. For example, Nelson and colleagues found that dropouts were more likely to deny needle sharing (associated with decreased rates of HIV

infection) but were also more likely to report being homeless and being younger (both associated with higher rates of HIV infection)(4).

Based on these previous results, we may find differential loss to follow-up by duration of injection. Shorter-term injectors may be more likely to drop out than longer-term injectors. If these dropouts are more likely to engage in riskier behavior, our data could underestimate the true difference between shorter-term and longer injectors.

7. Assessment of Interaction

As with the baseline analysis, interaction terms will be fitted to the models to investigate whether associations between the primary outcomes of interest (inject with others, inject more now, and no condom last time) and duration of injection differed by site of recruitment or race/ethnicity. The interaction terms will represent the product of the site or race/ethnicity variable (each category versus all other categories) by duration of injection.

Interaction will be assessed via formal tests of interaction on a multiplicative scale and through stratified analyses. The difference between –2log likelihood estimates of models with and without interaction terms will be compared to a chi-square distribution with degrees of freedom equal to the difference between the number of parameters in the two models. The interaction will be considered significant if the p-value is less than 0.05.

7. Statistical power

Estimates for the minimum odds ratios that can be detected in the baseline study are given in Table 3a. These estimates indicate that the study is adequately powered to detect odds ratios of 1.42, 1.45, and 1.56 for the main outcomes of interest (inject with others, inject more now, no condom last time, respectively) for the shorter-term injectors (0-1 years) compared to the longer-term users (4-6 years).

Table 3a also includes estimates for the minimum odds ratios for the interaction terms (duration of injection by site of recruitment and duration of injection by race/ethnicity) for the baseline study. Expected frequencies in the unexposed groups (4-6 year group) for the analysis of interaction were calculated by multiplying the expected frequency in the unexposed group hypothesized for the main effects model by the frequency of participants from the unexposed group (4-6 years) from each site of recruitment (or racial/ethnic group) specified.

Much larger sample sizes are needed for the detection of interaction terms. Smith and Day showed that even in optimal conditions -- if 50% of the study population is exposed to the risk factor and 50% is exposed to the effect modifier -- approximately 4 times as many subjects are needed as compared to the detection of the main effect (71). If the frequency of the exposure variable and the effect modifier are lower, an even greater sample size is required. Given the small expected frequencies for the unexposed group (4-6 years) after stratification by site (and separately by race/ethnicity), we are limited in our ability to detect effect modification in this study (minimum odds ratios range from 1.65 to 22.0). However, for our largest ethnic/racial group (White = 59% of the unexposed group) versus all other ethnic groups, we do have the ability to detect minimum odds ratios ranging from 1.65 to 2.1 (Table 3a).

It is our supposition that the follow-up results will confirm the findings from the baseline study and show that the shorter-term injectors (0-1 year) will engage in riskier injection practices and sexual behaviors than the longer-term users (4-6 years). However, we expect an overall decrease in the frequencies of the behaviors at the follow-up study for three groups, as discussed in the section on study limitations (Section 3.8). Therefore we hypothesize that the frequencies estimated for the baseline study will decrease by approximately 20% at the follow-up analysis. Given this information, the proposed follow-up study is adequately powered to detect associations ranging from 1.63 to 1.81 (see Table 3b). Given the decrease in the frequencies from the baseline to the follow-up study, we expect that the minimum detectable odds ratios for the interaction terms in the follow-up study will be even greater than for the baseline study, and thus our ability to detect effect modification for the follow-up analysis will be even more difficult.

Table 3a. Minimum detectable crude odds ratios for proposed baseline study of recent injection practices and sexual behaviors by duration of injection assuming alpha 0.05, power = 0.80, and ratio of unexposed (duration of injection = 4-6 years) to exposed (0-1 year) = 1.2:1

Outcome Variable	Expected Frequency of Outcome in the Unexposed Group (4-6 year group)	Frequency of Outcome in 0-1 year Group	Minimum Detectable Odds Ratio
"Inject with others"	56%	64%	1.42

Interaction: duration by site			
Baltimore	6%	28%	6.0
Chicago	12%	23%	2.3
Los Angeles	12%	23%	2.3
New Orleans	6%	28%	6.0
New York - Harlem	5%	26%	6.7
New York - LES	15%	28%	2.2
Interaction: duration by race/ethnicity			
White	33%	45%	1.65
Black	10%	28%	3.5
Hispanic	10%	28%	3.5
“Inject more now”	28%	36%	1.45
Interaction: duration by site			
Baltimore	3%	21%	8.5
Chicago	6%	18%	3.5
Los Angeles	6%	18%	3.5
New Orleans	3%	21%	8.5
New York - Harlem	3%	21%	8.5

New York - LES	8%	19%	2.7
Interaction: duration by race/ethnicity			
White	17%	27%	1.82
Black	5%	20%	4.8
Hispanic	5%	20%	4.8
“No condom last time”	15%	22%	1.56
Interaction: duration by site			
Baltimore	2%	20%	12.0
Chicago	3%	14%	5.0
Los Angeles	3%	14%	5.0
New Orleans	2%	20%	12.0
New York - Harlem	1%	18%	22.0
New York - LES	4%	13%	3.7
Interaction: duration by race/ethnicity			
White	9%	17%	2.1
Black	3%	17%	6.4
Hispanic	3%	17%	6.4

Table 3b. Minimum detectable crude odds ratios for proposed follow-up study of recent injection practices and sexual behaviors by duration of injection assuming alpha 0.05, power = 0.80, and ratio of unexposed (duration of injection = 4-6 years) to exposed (0-1 year) = 1.4:1

Outcome Variable	Expected Frequency of Outcome in the Unexposed Group (4-6 year group)	Frequency of Outcome in 0-1 year Group	Minimum Detectable Odds Ratio
"Inject with others"*	N/A	N/A	---
"Inject more now"	22%	32%	1.63
"No condom last time"	12%	20%	1.81

*Not applicable for follow-up survey because information regarding injecting with others was not collected at the follow-up study.

E. STUDY LIMITATIONS

Several study limitations should be acknowledged. In the first part of the analysis, we are planning to make inferences of longitudinal patterns based on serial cross-sectional data. Even after multivariate adjustment, these results must be considered with caution. The data collected are baseline data from the study participants, and represent information from only one point in time for each participant. Therefore, the use of serial cross-sections will not account for

individual changes over time. For this reason, we are conducting the follow-up study of these participants comparing incidence of riskier and safer behaviors by duration of injection. This will allow us to examine behavioral changes over time, and determine if these differences follow the time trends speculated in the cross-sectional study.

In addition, without a sampling frame, the extent to which this sample truly represents IDUs in general or even within the cities studied remains unknown. To offset this limitation, we will compare characteristics of our sample with relevant information from other data sets to explore this issue. In addition, inferences will be made with caution.

There also may be an issue regarding the validity of the information collected about behaviors in the last six months. Participants were asked to describe behaviors during the last six months. This assumes that behaviors are constant and there have been no dramatic changes during this period. If there had been, study participants' answers may reflect more recent patterns or an average of quite variable or extreme habits over this time period.

If participants differentially had periods where they stopped injecting this may have an impact on the findings. Duration of injection is calculated as the time between first injection and the date of interview, thus assuming that drug use is constant during this period. If longer-term users (IDUs of 2-3 years or 4-6 years) are more likely to have a period of no use, the cumulative exposure for these longer-term users may be quite similar to the exposure time for shorter-term users (IDUs of 0-1 year). Therefore, the results presented here may be a conservative estimate of the true difference in the behaviors of longer-term as compared to shorter-term users. However,

Nelson and colleagues, in a study of trends in HIV risk among IDUs, reported that 81% of the study participants had stable patterns of drug use during the study duration (up to 4 years) (4).

Changes in the frequency of risky behaviors during the course of the follow-up may occur. Participants received information at the baseline interview on methods for reducing risky behaviors associated with HIV, Hepatitis B, and Hepatitis C. Some participants are expected to report a decrease in this behavior from baseline to follow-up as a result of the study or based on previous knowledge of AIDS. Participants may also tend toward responses that are more socially desirable. More recent initiates may be more likely to minimize risky behaviors to impress the interviewer. Alternatively, longer-term injectors may be more likely to respond with more social desirable answers. Although this study did not include a social desirability scale, previous studies that have included a scale, including the original CIDUS study, have found that observed trends in behaviors were not affected by socially desirable responding(67, 72). Furthermore, by stratifying the analysis by duration of injection, we will be holding this expected overall decline in risky behavior among the study participants constant and focusing primarily on differential changes in behaviors by duration of injection -- the primary aim of the proposed second part of the analysis.

Finally, recent studies have reported declining risky behaviors including syringe sharing and backloading as well as increasing use of syringe exchange programs (72). Although, this information is, of course, an extremely positive development in the HIV epidemic among IDUs, such trends may result in dampening aspects of this proposed analysis. However, added understanding of risky behaviors among IDUs will assist in targeting appropriate prevention

efforts so further declines in seroprevalence can be attained. Unfortunately, the stability of such trends is uncertain and, thus, continued attention to defining the epidemic among IDUs is key to maintaining and advancing the decline in this high–risk population.

E. STUDY STRENGTHS

The current study has numerous strengths, one of which is its large sample size, which will increase the study's power to detect small associations. Use of a comprehensive, face-to-face interview-administered questionnaire will provide detailed and well-measured information on all variables measured, reducing misclassification and enhancing study precision.

Much of the research to date on IDUs has been based on convenience samples of IDUs in drug treatment programs. IDUs in treatment may vary significantly from untreated IDUs in terms drug use profiles and patterns of risk behaviors. It is estimated that only 15%-20% IDUs in the United States are enrolled in drug treatment at any given time, so studies based primarily on in-treatment populations may contain substantial biases. This proposed study will utilize a street-based sample of IDUs -- IDUs who do not interact with drug treatment programs and may have different risk behaviors and drug use patterns than the small percentage of IDUs enrolled in treatment. Thus, this study has the potential to provide useful information on the characteristics, HIV risk, and HIV exposure of a large proportion of IDUs that have been understudied by researchers in the past.

Not many studies have focused on the earlier part of the injection career. Shorter-term and younger injectors are often more difficult to reach and identify than longer-term users. This proposed study would be one of the few to utilize this younger population of injectors. Clearly, more detailed studies on the injection practices and sexual behaviors of younger injectors are necessary to understand and explain the high-risk among younger injectors.

In addition, few studies to date have examined specifically behavioral risks by duration of injection. A previous qualitative study found evidence that other injectors performed injection practices until the IDU developed competence for self-injection (65). Another study found that factors associated with HIV infection included needing a person to inject them at least 60 days beyond initiation of injection (16). While these studies are important, understanding how injection practices vary by duration of injection drug use must be better characterized.

Another strength of this proposed study is that it will provide more information on potentially modifiable behaviors. The results of this proposed study, in conjunction with those from other studies looking at young IDUs, may help reinforce the importance of prevention and education strategies for IDUs.

Finally, specifying risk behaviors that are common early during injection drug use would support the finding of increased rates of bloodborne infections found in previous studies and would indicate that injection risks are not merely progressive but reflect a typical early increase during the development of injection drug use, one that merits attention from prevention programs.

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APPENDIX B

Revised Specific Aims (January 2013)

SPECIFIC AIMS

While some studies looking at prevalent and incident HIV and other blood borne infections such as Hepatitis B and C have shown a proportionate and direct increase with duration of injection drug use, a number of other studies have suggested that the risk of infection is higher immediately following initiation. For example, Garfein et al., noted that the rates for Hepatitis B and C viruses rose precipitously within the first 2 years following initiation of injection (Garfein, AJPH, 1998). The discrepancies in patterns shown in previous studies may be due to the lack of comparability across studies with regard to recruitment methods or the calendar time when the study was conducted. This study, using a uniform design across several study sites during a specific calendar period, can provide additional insight to the ongoing dialogue.

This study will examine the prevalence of behaviors by duration of injection drug use to see if these behaviors parallel the literature of infection by duration. We hypothesize that newly, initiated IDUs are more likely to engage in riskier and less likely to engage in safer sexual behaviors and injection practices earlier in their injection career than during the later stages of their injection career. In addition, this study will examine race/ethnicity and site of recruitment by duration of injection, and we expected to observe differences by race with higher prevalence in blacks than whites.

These findings may provide additional insight into this ongoing debate about risk of infection during the early stage of an injection drug users' career and better inform the development of prevention strategies among young, newly initiated injection drug users.

The specific aims of the study are as follows:

1) Review the literature on methodological issues associated with studying young injection drug users, including sampling, measurement and design issues (Chapter 1)
2) Identify correlates and risk factors of HIV among young, newly initiated IDUs (duration of injection $\leq$ 2 years) and longer-term users (duration of injection > 2 years - 6 years), including demographic factors (age, sex, race, marital status, site of recruitment, etc), sexual behaviors (trading sex for money or drugs, IDU-partner, condom use, etc), and injection practices (sharing needles and equipment, frequency and location of drug use, etc.) and to compare and contrast the above correlates of HIV and HCV seroprevalence by duration of injection drug use (Chapter 2)
3) Examine the prevalence of HCV by duration of injection (0-1 year, 2-3 years, and 4-6 years) among individuals who injected for 6 years or less by race/ethnicity and site of recruitment, and examine ORs (and 95% CIs) for the association between prevalence and duration of injection, race, and site of recruitment and select demographic and injection behaviors (Chapter 3).

To address these aims, we plan to make use of questionnaire data from the Collaborative Injection Drug Users Study II (CIDUS II), a CDC-sponsored prospective study of young (18-29) and/or newly initiated IDUs (duration of injection < 6 years). The study was conducted at six sites in five United States (US) urban areas: Baltimore, Chicago, Los Angeles, New Orleans, and

New York City (Harlem and the Lower East Side). In this prospective study, investigators conducted risk interviews at baseline, and at two follow-up visits (6 month and 12 month) and obtained serum for HIV, HBV, HCV testing over a 2-year period.